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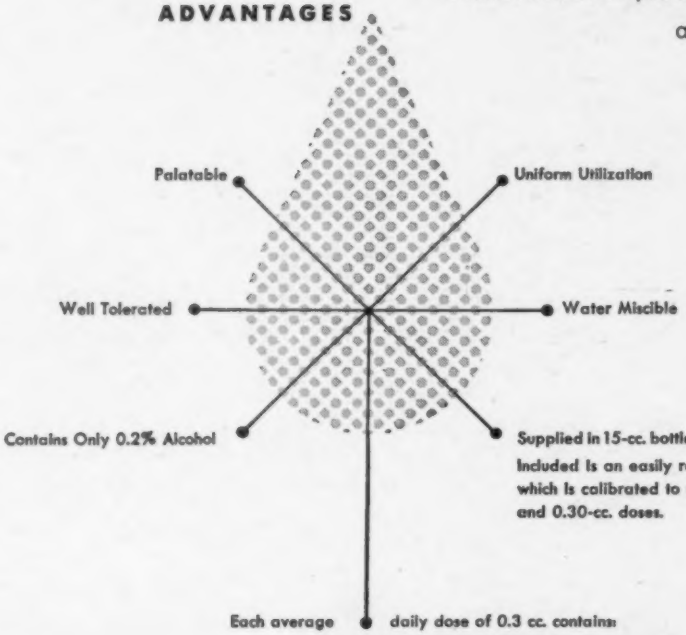
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Original Communications

GENERALIZED CYTOMEGALIC* INCLUSION DISEASE

J. P. WYATT, M.D., J. SAXTON, M.D., R. S. LEE, B.S., AND H. PINKERTON, M.D.
ST. LOUIS, MO.

THIS paper is concerned with a condition which in the past has been described under a variety of names: "inclusion disease," "generalized salivary gland virus infection," "salivary gland virus inclusion disease," "protozoan cell disease," and "fetal erythroblastosis." The diagnosis has invariably been made post mortem by finding the characteristic nuclear and cytoplasmic inclusions in various organs. The inclusions are identical with those found at autopsy in the salivary glands of from 10 to 32 per cent of all stillborn and living infants, regardless of the cause of death.[1, 2, 3]

The occurrence of inclusions in organs other than the salivary gland has been noted in from one to 2 per cent of unselected series of autopsies in infants.[1, 2] Including the six cases reported here however, only sixty-four cases of this type have been reported in infants, and two in adults.[4, 5] Mention should be made also of seven adult cases in which the characteristic inclusions have been found in biopsy and autopsy material from inflammatory lesions of the stomach,[6, 7, 8] esophagus,[9] and anal region.[10]

Although there has been a tendency in the past to regard these peculiar inclusions as an "incidental finding" in infants dying primarily from other causes, a careful analysis of recently reported cases, including those which will be reported here, indicates that the disease associated with the inclusions is usually the primary cause of death. In spite of the fact that the disease has not been transmitted to animals, there is practically conclusive evidence, which will be given in detail below, that it is a specific viral infection.

It is interesting to note that even recent textbooks of pediatrics, bacteriology, and virology do not discuss this condition. The main reasons for this omission probably are: first, a failure to recognize its importance (since it is largely a "pathologist's" disease), and second, the reluctance of many authorities to accept a disease as of established viral etiology in the absence of evidence of transmissibility to animals.

From the Department of Pathology, St. Louis University School of Medicine and the Snodgrass Laboratory of the St. Louis City Hospital.

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*Cytomegalic is derived from the term "cytomegalia" originally used by Goodpasture[25] in 1921 to indicate the bizarre cytological alteration characteristic of the disease to be incorporated into its name.

The disease may be found in the stillborn infant. As seen in living infants, it may be defined as an acute or subacute febrile illness, with a protean and as yet poorly outlined clinical picture, in which diagnosis is made by the presence of characteristic nuclear and cytoplasmic inclusions in various organs.

The purposes of this paper are to report six new cases of this condition, to attempt to delineate its clinicopathologic picture more clearly than has been done in the past, and to emphasize its importance as a fatal viral infection of fetal life and infancy.

CASE REPORTS

CASE 1.—Baby Y., a white male stillborn infant, was delivered at full term by breech extraction. The delivery was of the dry type and death of the infant apparently took place during parturition. The 25-year-old mother, gravida ii, para i, had premature separation of the placenta with this pregnancy and the previous one. Vaginal bleeding with her first pregnancy had been controlled by bed rest and progesterone. The first pregnancy had terminated in the delivery of a male infant, who died of respiratory difficulty four hours after parturition. No autopsy permission was obtained in the case of this first baby. Repeated serological investigation of the maternal serum was negative for syphilitic and Rh antibodies. The mother was Rh negative, the father Rh positive. There was no history of nutritional deficiency, infectious disease, or immunization during the course of either of the two pregnancies. Clinical diagnosis was stillbirth of unexplained etiology.

Gross Description.—The body was that of a full-term male stillborn infant showing generalized pallor of the skin and viscera and marked scrotal edema. The viscera were of normal size and weight and were free of any gross pathologic findings.

Microscopic Description.—The lungs showed a patchy peribronchial and septal inflammatory reaction. The inflammatory infiltrate consisted principally of lymphocytes and plasma cells. Atelectasis was found in both lungs, but expanded alveolar regions were frequent also, probably due to artificial insufflation at delivery. The placenta showed patchy calcification, but appeared otherwise normal. There was marked hematopoietic activity in the liver and spleen.

The characteristic inclusion-bearing cells (which will be described in detail later in the paper), were found in moderate numbers in the lungs and kidneys and in small numbers in the outer adrenal cortex. In the lungs, these cells were noted in the bronchiolar epithelium, apparently in the alveolar lining, and lying free in the alveoli. They were often, but not invariably, associated with the areas of septal inflammatory reaction.

In the kidneys, the large inclusion-laden cells occasionally filled the proximal convolutes; these portions of the nephrons were occluded also by albuminous and nuclear debris. A few focal collections of lymphocytes were found in the cortex, often surrounding inclusion-laden convoluted tubules. In the adrenals also, focal collections of lymphocytes occasionally were centered around inclusion-bearing degenerating cells, giving a picture like that seen in the salivary glands of infected animals.

The anatomic diagnoses made in all six cases will be listed below.

CASE 2.—Z. A., a 14-month-old female infant, previously normal and healthy, had difficulty in breathing, protracted coughing spells, and daily fever for eight days prior to hospitalization. Past history revealed that the child had received a diphtheria inoculation a few months prior to this fatal illness. This was the only child, and the mother had had no previous miscarriages. Radiologic examination revealed infiltration of both lower lobes of the lungs suggestive of lipoid pneumonia. Throat cultures were negative for the Klebs-Löffler bacillus. Blood cultures were negative. Marked cyanosis and convulsive vomiting developed in the hospital. The temperature remained constantly elevated above 102° F. A bluish-red maculopapular eruption was present over the thighs, back, and arms. Smears from these skin lesions showed no organisms. Eight days after the onset of illness, respira-

tions became markedly rapid and nuchal rigidity was noted. Despite oxygen and cardiac stimulants, death ensued. Clinical diagnosis was diffuse bronchopneumonia, postinfectional atelectasis, and meningismus.

Gross Description.—The body was that of a well-nourished white female infant 14 months of age. A bluish-red indurated maculopapular rash was noted over the back and arms. The glottis and larynx were pallid gray in color, edematous, and offered considerable obstruction to the laryngeal passageway. The lungs each weighed 80 grams and showed irregular dark blue firm regions scattered throughout all lobes. In the right middle lobe, yellowish areas were present which were definitely suggestive of pneumonic consolidation. The liver weighed 240 grams with a pale, moist, yellow cut surface and obliteration of markings.

Microscopic Description.—In both lungs there was an intense septal and peribronchial pneumonitis. The septal walls were diffusely involved, the principal calls being mononuclears. The bronchioles contained neutrophiles, lymphocytes, and macrophages intermingled with the desquamating epithelial cells. Although few in number, the inclusion-laden cells were seen in the midst of the mononuclear inflammatory infiltrates, particularly in the regions of septal involvement.

In the kidney there was cloudy swelling of the tubules with isolated inclusion-laden cells in the proximal convoluted tubules. The glomeruli, interstitial tissue, and vessels were negative. In the liver and spleen there were collections of mononuclear cells, but otherwise these tissues were negative.

Examination of the glottis showed subepithelial edema with a few mononuclear cells. The epithelium was intact. No cells bearing inclusion bodies were found. Heart, bone marrow, and adrenals were negative.

CASE 3.—M. R., a 14-month-old female Negro infant, had entrance complaints of whooping cough for three weeks, fever, and convulsions. The latter two symptoms had been present for eight days prior to hospitalization. This infant had had no previous illnesses. A brother of this child had suffered from whooping cough at the same time. Recovery had been prompt. The mother had had two other children, both now dead. These children had died a year previously, one apparently from whooping cough and the other from tuberculosis.

Physical examination of this acutely ill infant revealed moderate dehydration and an elevated temperature. No diphtheria bacilli were recovered from the acutely inflamed throat. Roentgenologic examination of the chest revealed slight accentuation of peribronchial markings but no conclusive evidence of shadowing within the lung fields. Condition in the hospital progressively became worse, with labored respirations, bronchial breathing over the left lung, convulsions, and peripheral circulatory collapse. Oxygen, sulphathiazole, alpha-lobeline, and intravenous glucose were of no avail, and the patient died one month after onset of the illness. Clinical diagnosis was whooping cough and diffuse atypical bronchopneumonia.

Gross Description.—The body was that of a Negro female infant, 14 months of age, weighing 4,000 grams. Apart from the gross pathologic changes of the lungs, there were no pertinent macroscopic observations. The sizes and weights of the viscera were within normal limits.

The right lung weighed 60 grams and the left 40 grams. The external surfaces were smooth, glistening, and red. The bronchi were free of exudate. The cut surfaces were dark red, noncrepitant, smooth, and a slight watery yellow exudate was noted on compression.

Microscopic Description.—Within the lungs there was a diffuse intense septal pneumonitis with the inflammatory exudate made up principally of lymphocytes and mononuclear cells. Throughout the invloved septas there were scatterings of the characteristic huge swollen cells with large ovoid or reniform nuclear inclusions and basophilic cytoplasmic dots. (Fig. 8.) As many as five affected cells per high-power field, situated in the midst of the mononuclear infiltrations, were discovered. The affected cells were found also in bronchiolar mucosa and swollen alveolar walls. No giant cells were encountered.

Within the liver, nucleocytoplasmic inclusion bodies were found exclusively in the parenchymal cells. Around isolated hepatic cells laden with the specific inclusions were groups of

neutrophilic leucocytes and monocytes. Fatty metamorphosis in the centrilobular zone was present in addition to the intersinusoidal mononuclear infiltrations.

Involutional change within the thymus was pronounced. Pancreas, spleen, marrow, and adrenals were negative.

CASE 4.—R. R., a 13-week-old white male infant, was first admitted to the hospital five days after birth with diffuse skin purpura and an enlarged liver and spleen. There had been no previous pregnancies. Both mother and baby were Group A Rh positive. There was no accumulation of Rh antibodies in the mother's serum. No familial history of blood diseases was obtained. Serologic tests for syphilis in the infant, mother, and father were negative. Hematologic studies on this admission revealed a red-cell count of 2,400,000, with a few erythroblasts in the smear and a platelet count as low as 80,000 per cubic millimeter. Urinalysis was repeatedly negative. A clinical diagnosis of congenital thrombocytopenic purpura was made. Infusions of concentrated compatible red blood cells were given. The infant was discharged with improvement in clinical signs but persistence of hepatosplenomegaly. Second admission three weeks later revealed an elevated temperature, frequent bloody stools, vomiting of fresh blood, and nonprotein nitrogen of 54 mg. per cent. The enlarged spleen and liver were more noticeable. The white blood cell count slowly increased from 11,000 to 30,000 per cubic millimeter with an absolute increment in metamyelocytes and myelocytes. Fifty-three erythronormoblasts per 100 white blood cells were noted in the smear. The platelet count remained around 40,000 per cubic millimeter with a normal bleeding and clotting time. Frequent bloody stools enhanced the dehydration. Despite repeated compatible bank blood transfusions, the anemia remained severe with counts as low as 2,100,000 red blood cells. Bone marrow aspiration revealed a normal differential for an infant of this age. Labored respirations, cyanosis, and disseminated purpura were pronounced immediately prior to death. Clinical diagnosis was thrombocytopenic purpura and diarrhea, cause undetermined.

Gross Description.—The autopsy was performed on a markedly dehydrated, poorly nourished, 13-week-old white male infant. The fontanels and eyeballs were collapsed. The liver weighed 85 grams, was firm in consistency with discrete red-gray patches on a dark brown background. The spleen weighed 30 grams, was firm and dark red in color. The terminal ileum contained several mucosal erosions, averaging about 2 mm. in diameter. The kidneys were not enlarged. Their cortices were pallid, smooth, and sharply demarcated from the brownish-red medullas. No other pertinent macroscopic observations were made.

Microscopic Description.—The liver architecture was preserved, with an occasional focus of granulocytic and normoblastic cells within the sinusoids. The inclusion-laden cells were sparse in number and almost exclusively situated in the bile duct channels. A few granules of hemosiderin were found in the hepatic and Kupffer cells.

Within the lungs there was an irregular mononuclear septal pneumonitis. An occasional characteristic large cell with nuclear and cytoplasmic inclusions was noted. No bacteria were demonstrated with a Gram stain.

In the kidney a large proportion of the proximal convoluted tubules showed widespread involvement of the epithelium (Fig. 1). The cells were gigantic in outline, and in places the lumens were occluded completely by the nests and clusters of the singularly large cells burdened with inclusions. Surrounding many of these altered tubules were infiltrates of mononuclear cells. Hemosiderin dust was noted in association with these infiltrations. The glomeruli and vascular elements were negative.

The subependymal regions of the brain showed a number of swollen, necrotic astrocytes laden with the specific inclusions. These cells were surrounded by a microglial reaction. Deep to the ependyma there was a dense astrocytic network and diffuse calcification. Lymphocytic and microglial cuffing was present.

In the pancreas a few acinar cells bore characteristic nuclear and cytoplasmic inclusions. In the ileum there was an inflammatory reaction in the Peyer's patches, with many inclusion-laden mononuclear cells and ulceration of the epithelium. The myocardium, lymph nodes, and thymus were free of pathologic alterations.

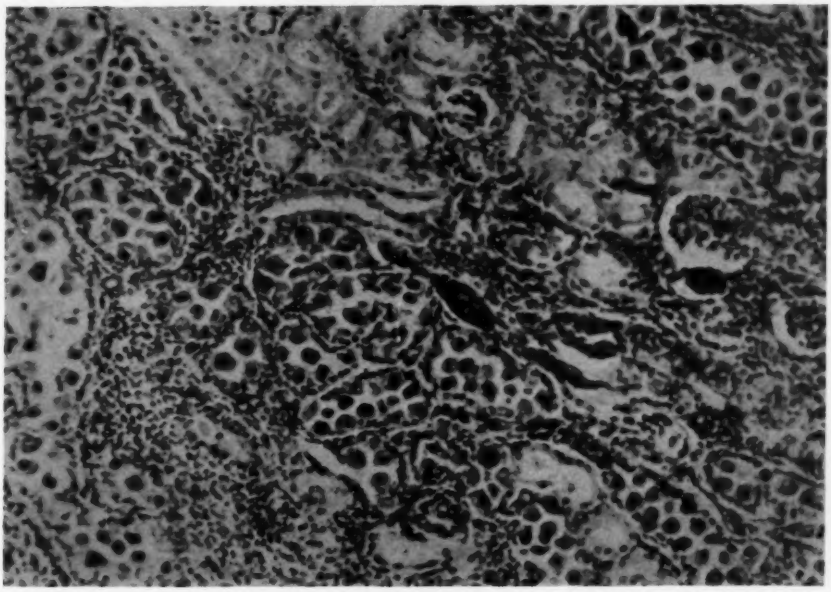

Fig. 1.—Kidney, showing widespread desquamation of swollen, vacuolated and degenerating, inclusion-laden cells into tubules. Note the marked inflammatory cell reaction. Normal tubules are included above for contrast. Case 4. Hematoxylin and eosin. (×180)

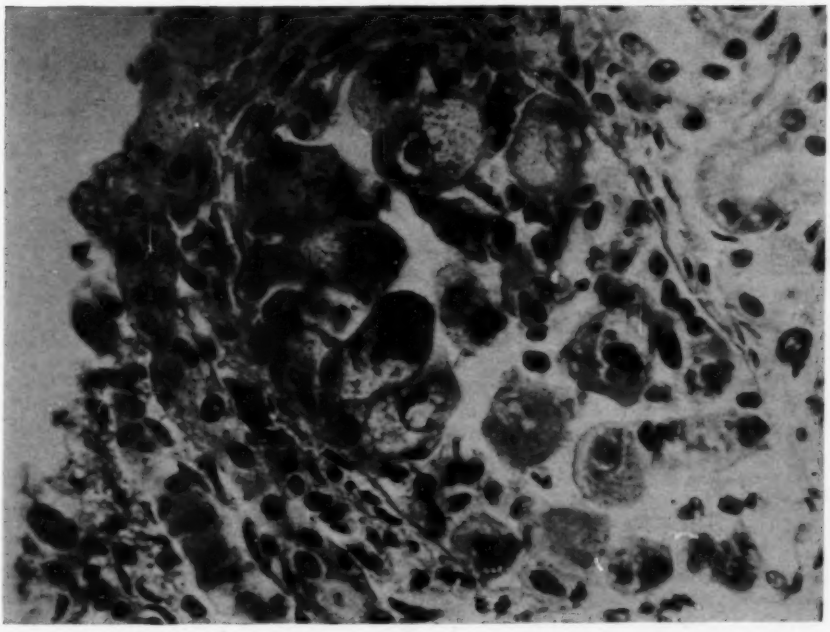

Fig. 2.—Kidney, with renal tubule epithelial cells, showing various stages in the development of inclusions, and degeneration and desquamation of affected cells. Case 6. Hematoxylin and eosin. (×430)

CASE 5.—C. D., a 7-week-old male infant, second child in the family, was hospitalized on the first admission for acute otitis media and nasopharyngitis. No history of previous immunization, injections, or exposure to contagious disease could be obtained. Liver, kidneys, and spleen were not palpable on this admission. Penicillin was originally given, then sulfathiazole and sulphadiazine were instituted for the upper respiratory tract infection. Sulphadiazine therapy was discontinued after four days because of transitory crystalluria. Red blood cell count on this admission was 4,000,000 per cubic millimeter, white blood cell count 13,000 per cubic millimeter, and hemoglobin 12.0 Gm. The blood Kahn was negative. The otitis media and nasopharyngitis subsided, and the patient was discharged. The second admission followed a week later, because of frequent bowel movements of a yellow, watery nature. The infant was dehydrated, and the degree of acidosis was indicated by a carbon-dioxide combining power of 29 volumes per cent. Despite varied supportive and chemotherapeutic agents, hematemesis and melena developed and continued. Family history obtained at this time showed that the mother had had two spontaneous miscarriages, and one child was living. One of the siblings on the father's side was said to have died of pneumonia in infancy. Mother and infant were both Group O Rh positive.

Course in hospital was characterized by a progressive hepatosplenomegaly, low-grade fever, pronounced anemia of 3,200,000 red blood cells, and during the last days of life a severe jaundice. The iceteric index climbed to 150 units with the direct van den Bergh positive and the indirect reading 9.4 mg. per 100 cubic centimeters. Prothrombin time was 75 per cent of normal; capillary fragility was not increased. In the last week in hospital, generalized edema, oliguria, massive hematuria, and pronounced recurrent ascites developed. The white blood cell count was 22,500 per cubic millimeter with many young granulocytes, and the occasional nucleated red blood cell. The total plasma protein reading was 4.9 Gm., globulin contributing 2.2 Gm. Bile in the urine was repeatedly positive. Stool culture was negative for pathogens. Paracentesis, blood transfusions, cortin, liver, and antibiotics were of no avail, and the infant succumbed eighteen days after the second admission. Clinical diagnosis was virus hepatitis and enteritis.

Gross Description.—This 7-week-old white male infant showed pronounced abdominal distention at necropsy. The heart, lungs, adrenals, kidneys, spleen, and brain were not remarkable. The abdomen contained approximately 250 c.c. of straw-colored fluid. The liver weighed 190 grams with a smooth, glistening, taut capsule. Cut surface was of a dark rust-red color and firm consistency. No other pertinent findings were noted.

Microscopic Description.—Microscopic examination of the liver revealed considerable disorganization of the lobular architecture. The liver cells, particularly in the centrilobular zones, were undergoing profound degenerative changes associated with sinusoidal congestion and erythrocytic extravasation. In many of these zones there was complete liver cell necrosis with only extracellular bile and hemosiderin pigment, polynuclear collections, and cellular detritus remaining. Many of the liver cells showed their canaliculi plugged with bile. The fibrosis was recent in origin and principally periportal in distribution with fibroblastic proliferation passing between and around the liver cords. The cells containing inclusions were found in this case almost exclusively in the autolytic hepatic cells. (Fig. 7.) The over-all picture was that of a diffuse hepatitis and hepatic fibrosis of recent genesis.

In the spleen there was atrophy of the lymphoid follicles and within the sinusoids there were discrete myelopoietic islands. Groups of polynuclear neutrophiles were encountered both in the pulp and in the Malpighian corpuscles.

Although only a few inclusion-laden cells were seen in the swollen septa, there was a diffuse interstitial pneumonitis with a predominantly mononuclear exudate. In the basal portions of the lung there was a superimposed intra-alveolar polynuclear exudate, adjacent bronchioles containing neutrophilic leucocytes, and fibrin.

Both pancreas and kidney showed a sparse number of the specifically altered cells with associated lymphocytic foci. In the brain several isolated inclusional bodies within neuroglial nuclei were found beneath the ependyma of the lateral ventricles. No glial nodules were noted in association with these structures. The remainder of the central nervous system was negative to microscopic examination.

The myocardium, adrenals, lymph nodes, bowel, and thymus were negative.

CASE 6.—This newborn white female infant was delivered of a 21-year-old Rh-negative mother. Due to the diffuse purpura over the entire body and the pronounced hepatosplenomegaly, this infant was transferred immediately to the pediatric service. This was the mother's second child. Her first-born was 2 years old and in good health. The father was Rh positive, the newborn infant Rh positive. The blood Kahn in the mother and the infant were negative. Immediately after delivery the red-cell count was recorded as 4,800,000 per cubic millimeter, hemoglobin 18 Gm., and the white cell count was 26,650 per cubic millimeter. Differential revealed 3 per cent erythroblasts, 15 per cent normoblasts, intense polychromatophilia, and an inadequate number of platelets. Platelet count four days later was noted as 23,000 per cubic millimeter. Bleeding time was markedly prolonged, reticulocyte count was 13.3 per cent and prothrombin time 100 per cent. Icterus, purpura, and cyanosis all progressively increased in intensity in the hospital. Diarrhea with yellow-green stools was reported ten days after birth. Stools and serum were negative for pathogens of the typhoid-paratyphoid group. Throughout the course of this fatal illness in the hospital there was a constant elevation of temperature up to 102° F. The red cell count remained constantly above 4,500,000 and the hemoglobin above 15 Gm. After the initial birth leucocytosis, the white cell count remained around 11,000. Urinalysis revealed urobilinogen to the dilution of 1:20 and bilirubin strongly positive. The cephalin flocculation test two weeks before death was 4 plus. This infant received numerous small compatible transfusions, although anemia was not present. The platelets remained profoundly depressed. The infant became progressively worse, with deepening of jaundice and spreading of the purpura. Intense dehydration with acidosis indicated by a carbon-dioxide combining power of 33 volumes per cent was noted. Despite blood transfusions, choline, intravenous Ringer's solution, vitamin K, and oxygen, this infant died five weeks after birth.

Gross Description.—This was a well-developed female baby weighing 2,635 grams. Generalized icterus, abdominal distension, and widespread purpura were dominant. One hundred cubic centimeters of yellow fluid were present in the abdomen. The lungs, heart, adrenals, kidneys, thymus, thyroid, and brain were not remarkable. The gastrointestinal serosa was splashed with purpuric blotches with the mucosa red and granular. The liver weighed 250 grams and was finely nodular, firm in consistency, with a rust-brown cut surface, and numerous purple blotches throughout. The dark red spleen, 80 grams in weight, presented increased resistance on cutting, with obliteration of Malpighian bodies.

Microscopic Description.—A few proximal convoluted tubules in the kidney contained affected cells. The lumens of these tubules were plugged with degenerating inclusion-laden cells and protein debris. Granules of hemosiderin were noted within the distal convoluted tubules. Both lungs microscopically showed swelling of all septas with lymphocytes, mononuclears, eosinophiles and distorted fibroblastic nuclei. A few isolated inclusion-bearing cells were noted, particularly in the areas in which the alveolar walls were most intensely infiltrated with mononuclears. Neither polynuclears, fibrin, nor protein fluid were found within the alveoli.

There was considerable disorganization of the liver architecture. In the peripheral and central zones the hepatic cells were undergoing degenerative changes. (Fig. 6.) The fibrosis was extensive and recent, in some regions extending to the central vein, giving a monocellular pattern. Many of the biliary channels contained the afflicted cells, and their lumens were occluded by these huge cells. The lumens were frequently plugged with inspissated bile. Only a few hepatic cells revealed the characteristic nuclear and cytoplasmic structures, although groups of regenerative liver cells had fused together, producing bi- and tri-nucleate giant cells. In the periportal zones, bile duct proliferation and foci of granulocytes and mononuclears were noteworthy. Extramedullary hematopoiesis, principally sinusoidal in situation, also was evident.

In the spleen there was a fine diffuse reticular fibrosis with numerous scattered groups of hematopoietic elements, in which both red and white cell lineages were represented. Inclusional cells were noted in the pancreatic acini, intermingled with sparse collections of lymphocytes and mononuclear cells. Within the brain there were a few glial foci beneath the ependyma, probably representing imperfect differentiation. Calcific granules in these regions were

noted. The remainder of the microscopic examination of the brain was not remarkable. A few specifically altered cells with inclusions distorted an occasional thyroid acinus; several swollen inclusion-burdened cells were discovered in the parathyroids. There was myeloid hyperplasia of the marrow. The myocardium, adrenals, thymus, and lymph nodes were negative.

Morphology and Cytology of the Inclusion-Bearing Cells.—Since the abnormal cells and their inclusions are identical in appearance in all sites and in all cases, only a composite description will be given. This delineation is best exemplified by the changes in the kidney in Case 4 (Figs. 1 and 3), and in the kidney and liver of Case 6 (Figs. 2 and 6). Few evolutive forms were seen although numerous degenerative examples were found. The change in cell size and contour was of the "all or none" variety, and the volumetric nuclear/cytoplasmic ratio remained relatively constant.

The affected cells measured up to 35 μ in diameter. The nuclei of the involved cells contained bright acidophilic or at times equivocally stained inclusions. These bodies stained red with Masson's trichome, black with iron hematoxylin, were unstained by acid-carbol fuchsin, and stained red with periodic acid. These nuclear inclusions (Fig. 2) frequently contained a homogenous central core and a dusty peripheral zone. Two distinct inclusions were occasionally seen in the same nucleus, but larger numbers were not encountered. These nuclear inclusions reached a size up to 15 microns in diameter. Outside of the well-formed intranuclear structure there was a clear halo in the nucleoplasm. Outside of this again was the well-demarcated nuclear membrane bearing several condensed basophilic beads or "orbital or polar bodies" (Fig. 3) as described by Cappell[31] and MacMillan.[5]

The cytoplasmic changes in the damaged cells were less common than the nuclear changes. The basophilic bodies were most frequently encountered in cells which also contained nuclear inclusions. The presence of cytoplasmic bodies in cells without visible nuclei may be due to artefactual exclusion of the nucleus in sectioning these huge cells. The cytoplasm usually was swollen and vacuolated (Fig. 2), containing up to twenty-minute basophilic inclusional structures ranging from 2 to 4 microns in diameter (Fig. 4). These bodies tended to be localized in one portion of the cytoplasm or at the peripheral borders (Fig. 2) as if ready to escape from the cells. These cytoplasmic bodies enhanced the distortion of the cell contour. An excellent morphological description of these cytoplasmic inclusions is found in the contribution of Cappell and McFarlane.[31] Although special stains will heighten the chromatism of the inclusion bodies, standard hematoxylin and eosin dyes are satisfactory for their demonstration.

Two further features of diagnostic importance should be noted. The presence of these swollen singular cells stuffed with disintegrating inclusional debris (Fig. 7) in desquamates (Fig. 2) or in inflammatory debris (Fig. 8) is highly characteristic. The other cardinal lesion is the presence of swollen cells (Figs. 6 and 8) showing nuclear polymorphism, hypertrophy, and smudges of cytoplasmic granules. The presence of these two lesions should be regarded as stigmata of inclusion disease with the implication that a more detailed histopathologic examination will uncover the specific inclusions.

Anatomic Diagnosis.—

CASE 1: Full-term white male stillborn infant; nuclear and cytoplasmic inclusions of salivary gland virus type in lungs, kidneys, and adrenals; atelectasis of all lobes of both lungs; minimal interstitial pneumonitis; embryonic blood formation in liver and spleen; hyalinization and calcification of mature placenta.

CASE 2: Nuclear and cytoplasmic inclusions of Farber and Wolbach[2] in lungs and kidneys; interstitial pneumonitis; focal bilateral atelectasis; mononuclear infiltration of liver; edema of glottis; maculopapular rash of arms, thighs, and back.

CASE 3: Nuclear and cytoplasmic inclusions in lungs and liver; interstitial pneumonitis; mononuclear infiltration of liver; sulphonamide crystals in renal pelves.

CASE 4: Generalized visceral involvement with nucleocytoplasmic inclusions in kidneys, liver, lungs, pancreas, ileum, adrenals, and brain; severe nephrosis; septal pneumonia; extramedullary hematopoiesis of liver and spleen, subacute sclerosing ependymitis.

CASE 5: Diffuse inclusion disease of liver, lungs, pancreas, brain, and kidney; portal cirrhosis; extramedullary hematopoiesis of liver and spleen; interstitial pneumonitis; bilateral bronchopneumonia.

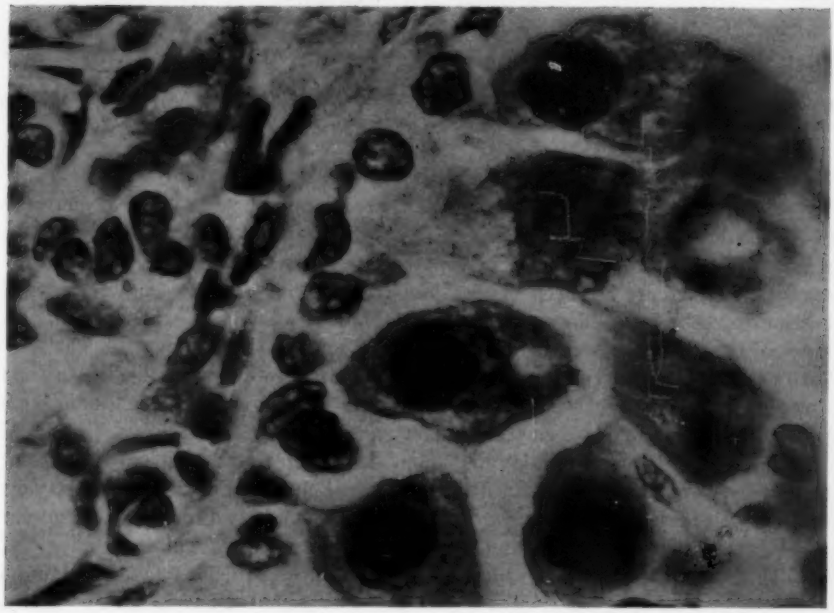

Fig. 3.—Kidney, showing altered renal tubule epithelial cells. Large granular intranuclear inclusions surrounded by a clear zone. Two beads of condensed chromatin in the nuclear membrane. Coarse smudged intracytoplasmic inclusions also present. Case 4. Hematoxylin and eosin. (×960)

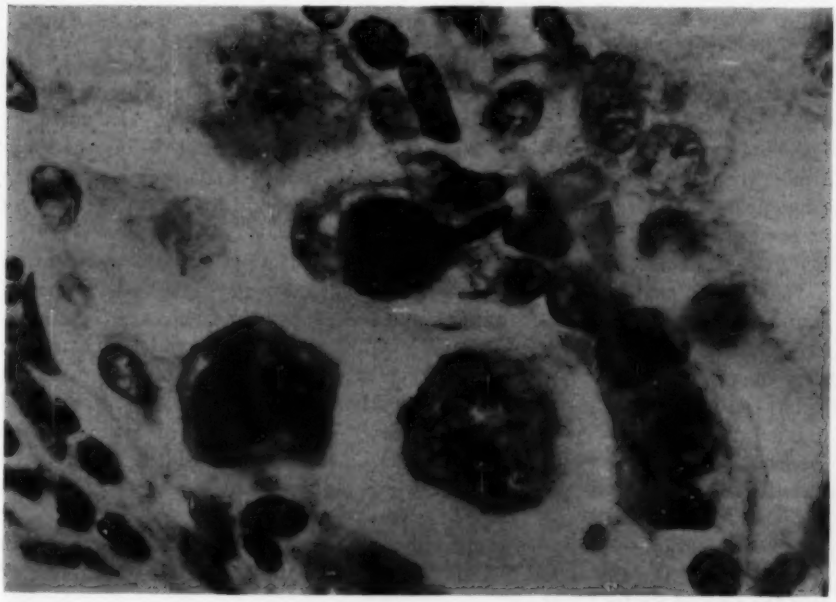

Fig. 4.—Renal tubule cells with coarse intracytoplasmic inclusions, nuclear inclusions, and a degenerating cell. Case 5. Hematoxylin and eosin. (×930)

CASE 6: Disseminated salivary gland virus inclusions in salivary gland, liver, kidneys, lungs, pancreas, thyroid, and parathyroid; hepatosplenomegaly; obstructive biliary cirrhosis; pronounced bile stasis; ascites; interstitial pneumonitis; marked myeloid hyperplasia of bone marrow; persistent autochthonous myelopoiesis in liver, spleen, and kidney.

TABULATION OF REPORTED CASES

The presence of inclusions in the salivary glands of from 10 to 32 per cent of infants dying from various causes[1, 2, 3] indicates that the infection exists in a latent or asymptomatic form. We are concerned here primarily with those cases in which there has been visceral involvement. Even if we confine our discussion to these cases, however, we must include a number in which the importance of the viral infection as a cause of illness and death is unknown. The stillborn cases, whether premature or full-term infants, are difficult to evaluate from this point of view, and the same is true of those cases in which other lesions were present which may have been the primary cause of death.

All reported cases in which inclusions have been found post mortem in one or more viscera are included in Table I. It will be noted that of the sixty-six cases in this series, sixty-four were in infants and only two in adults. The visceral distribution of the inclusions in these cases is shown in Table II.

The seven adult cases in which the characteristic inclusions have been found in biopsy and autopsy material from the gastrointestinal tract (ulcerative lesions in six cases and a tumorlike lesion in one case) are shown in Table III. These interesting cases are placed in a separate category because their significance in relation to the general picture is not yet clear.

The discussion on the clinical and pathologic findings in these cases will follow.

INCIDENCE AND GEOGRAPHIC DISTRIBUTION

As has already been noted, the latent form of the infection, which is recognized by the presence of inclusions only in the salivary glands, was noted by Farber and Wolbach[2] in 12 per cent of 183 consecutive autopsies at the Childrens' Hospital in Boston; by McCordock and Smith[1] in 10 per cent of sixty consecutive autopsies on stillborn and living infants; and by Prawirohardjo[3] in 32 per cent of routine pediatric autopsies.

The incidence of the visceral form of the infection was 1.2 per cent in Farber and Wolbach's series[2] of 183 unselected autopsies on infants under 17 months of age, and 2.1 per cent in a similar study of ninety consecutive autopsies reported by McCordock and Smith.[1] Our experiences parallel those of the above-mentioned workers, since five of the six cases reported here were found to have occurred in a series of 461 consecutive autopsies done on stillborn and living infants under 5 years of age at the St. Mary's group of Hospitals and the St. Mary's Infirmary; an incidence of 1.1 per cent. The sixth case occurred recently in the St. Louis City Hospital, where statistical studies of this condition have not been made.

The infection seems to be geographically widespread, examples having been reported from the Continent,[12] England,[31] Dutch Indies,[9] China,[32] Canada,[5, 39] and the United States.[1, 2, 30]

TABLE I. SIXTY-SIX REPORTED CASES OF INCLUSION DISEASE

CASE	YEAR	AUTHOR	AGE AND SEX*	CLINICAL OR AUTOPSY OBSERVATIONS	ORGANS INVOLVED
1	1904	Jesionek and Kiolemenoglou[11]	Stillbirth	Congenital syphilis	Kidneys, lungs, liver
2	1904	Ribbert[12]	Newborn	Congenital syphilis	Kidneys
3	1910	Pisano[13]	Stillbirth	Congenital syphilis	Kidneys, lungs, liver
4	1911	Mouchet[14]	8 days	Congenital syphilis; icterus	Liver
5	1911	Pettavel[15]	10 days	Purpura	Thyroid
6	1910-1911	Smith and Weidman[16]	Stillbirth	Focal nephritis; "entamoeba mortinatalium"	Kidneys, lungs, liver
7	1914	Smith and Weidman[17]	2 months	Congenital syphilis; pneumonia; "entamoeba mortinatalium"	Lungs
8	1921	Goodpasture and Talbot[18]	6 weeks male	Bronchopneumonia; anemia	Kidneys, lungs, liver
9	1922	Jackson[19]	15 months male	Diphtheria; bronchopneumonia; parenchymatous nephritis	Kidneys
10	1922	de Lange[20]	8 days	Congenital syphilis; icterus; cirrhosis of liver	Kidneys, lungs
11	1922	Müller[21]	Stillbirth		Kidneys
12	1922	Müller[21]	8 weeks	Hydrocephalus; interstitial nephritis	Kidneys
13	1922	Müller[21]	2 months	Congenital syphilis	Kidneys
14	1925	von Glahn and Pappenheimer[4]	36 years male	Ulcerative colitis; liver abscess; lobar pneumonia	Lungs, liver, intestines
15	1926	Walz[22]	Newborn	Prematurity; asphyxia	Kidneys, lungs, liver, thyroid, pancreas
16	1927	Feyrter[23]	2½ months	Pertussis	Lungs
17	1930	Wagner[24]	2 weeks	Prematurity	Kidneys, lungs, liver, pancreas, thyroid, epididymis, sublingual gland
18	1932	Farber and Wolbach[2]	20 days, female	Hemorrhagic diathesis	Kidneys, lungs, liver, pancreas, thyroid
19	1932	Farber and Wolbach[2]	2 days, male	Erythroblastosis	Kidneys, lungs, pancreas, liver
20-24	1932	Rich[25]	2½ months to 2 years	Pertussis	Lungs
25	1933	Wanstrom[26]	6 hours, female	Fetal erythroleucoblastosis	Kidneys, liver
26	1934	McCordock[1, 27] and Smith[1]	4 months	Pancreatic fibrosis; chronic pneumonia	Lungs
27	1934	McCordock and Smith	3 months	Pancreatic fibrosis; chronic pneumonia	Lungs, liver, adrenals, kidneys
28	1934	McCordock and Smith	4½ months	Chronic pneumonia	Lungs
29	1934	McCordock and Smith	5 months	Chronic pneumonia	Lungs
30	1934	McCordock and Smith	2 years	Chronic pneumonia; gangrene of face, gums, palate; ulcerative colitis	Lungs
31	1934	McCordock and Smith	3 months	Chronic pneumonia	Lungs
32	1934	McCordock and Smith	Newborn	Erythroblastosis	Lungs
33	1934	McCordock and Smith	6 months	Cerebral hemorrhage	Liver (few)
34-53	1934	McCordock and Smith	Newborn to 5 years	Pertussis and two controls	Lungs, liver, adrenals

*Sex not known if not stated in table.

(Continued on next page.)

TABLE I—CONT'D

CASE	YEAR	AUTHOR	AGE AND SEX*	CLINICAL OR AUTOPSY OBSERVATIONS	ORGANS INVOLVED
54	1935	Andrews and Miller[28]	Newborn, female	Erythroblastosis	Kidneys, lungs, skin
55	1940	Vidari[29]	Newborn	Icterus neonatorum; erythroblastosis	Kidneys, lungs, liver, thyroid
56	1942	Kinney[30]	14 days, female	Erythroblastosis	Kidneys, lungs, liver, pancreas, brain
57	1947	Cappell and McFarlane[31]	Newborn, male	Hemolytic disease with no evidence of maternal isoimmunization	Kidneys, lungs, liver, pancreas
58	1947	Cappell and McFarlane[31]	Newborn	Hemolytic disease with no evidence of maternal isoimmunization	Kidneys, liver
59	1947	McMillan[5]	60 years, female	Inclusion disease pneumonitis; vitamin A deficiency	Lungs, adrenals
60	1947	Kalfayan[54]	2½ months, male	Conjunctivitis, interstitial pneumonia, hepatitis	Eyeball, salivary gland, thyroid, lungs, liver, adrenal, kidneys, pancreas, spleen
61	1949	Wyatt, Lee, Saxton, and Pinkerton	Stillborn, male	Atelectasis; interstitial pneumonitis; disseminated inclusions	Lungs, kidneys, adrenals
62	1949	Wyatt, Lee, Saxton, and Pinkerton	14 months, female	Atypical pneumonia; disseminated inclusions, interstitial pneumonitis	Lungs and kidney
63	1949	Wyatt, Lee, Saxton, and Pinkerton	14 months, female	Whooping cough; disseminated inclusions; interstitial pneumonitis	Lungs and liver
64	1949	Wyatt, Lee, Saxton, and Pinkerton	13 weeks, male	Thrombocytopenic purpura; disseminated inclusions; severe nephrosis, ependymitis, ileitis	Kidneys, liver, lungs, pancreas, adrenals, brain, ileum
65	1949	Wyatt, Lee, Saxton, and Pinkerton	7 weeks, male	Viral hepatitis and enteritis; disseminated inclusions; portal cirrhosis	Liver, lung, pancreas, brain, kidneys
66	1949	Wyatt, Lee, Saxton, and Pinkerton	5 weeks, female	Acute hepatic insufficiency; disseminated inclusions; biliary cirrhosis	Liver, lungs, kidneys, pancreas, thyroid, parathyroid, salivary gland

*Sex not known if not stated in table.

TABLE II. VISCERAL DISTRIBUTION OF INCLUSIONS IN THE SIXTY-SIX CASES

ORGAN	FETUSES AND INFANTS (64 CASES)	ADULTS (2 CASES)	TOTAL (66 CASES)
Kidneys	27/64	0/2	27/66
Respiratory tract	52/64	2/2	53/66
Liver	21/64	1/2	22/66
Thyroid	7/64	0/2	7/66
Pancreas	10/64	0/2	10/66
Gastrointestinal tract	1/64	1/2	2/66
Epididymis	1/64	0/2	1/66
Skin	1/64	0/2	1/66
Brain	3/64	0/2	3/66
Adrenals	6/64	1/2	7/66
Spleen	1/64	0/2	1/66
Eyeball	1/64	0/2	1/66

TABLE III. CASES OF LOCALIZED INCLUSION DISEASE IN ADULTS

YEAR	AUTHOR	CLINICAL OBSERVATION	ORGAN
1935	Hartz[6]	Peptic ulcer	Stomach
1935	Hartz[6]	Peptic ulcer	Stomach
1935	Hartz[6]	Peptic ulcer	Stomach
1936	Hamperl[7]	Peptic ulcer	Stomach
1937	Soeharto[8]	Peptic ulcer	Stomach
1941	Hartz and van der Sar[9]	Ulcer	Esophagus
1943	Hartz and van de Stadt[10]	Inflammatory tumor	Anus

EPIDEMIOLOGY

The occurrence of the disease in stillborn and premature infants makes it necessary to assume that infection is acquired from the mother during intrauterine life. The virus probably is present in a latent form in many adults, and frequently localizes in the salivary glands of infants in utero. The conditions under which the infection becomes generalized and causes fatal illness are not known. The epidemiological problems involved appear to be similar to those which exist in toxoplasma infection. Examination of the placenta in Cases 2 and 5 showed no inclusions.

The analogous disease in the guinea pig does not, as far as we know, occur spontaneously in a generalized form. Guinea pigs acquired from some breeders will be found to be free from salivary gland virus infection, while other herds may be almost uniformly infected. There is evidence that guinea pigs which do not carry the virus in a latent form are somewhat more susceptible to the virus than are guinea pigs from a latently infected strain, and certain strains of the virus appear to be much more virulent than others.[33]

ETIOLOGY

The developmental history of etiological concepts concerning this disease has resulted in much confusion. It is not surprising that the bizarre appearance of inclusion-bearing cells should have led early investigators of high repute to regard them as protozoa (Ribbert,[12] 1904, and Smith and Weidman,[16, 17] 1910 and 1914). In 1921 Goodpasture[18] published evidence that the peculiar cells were derived from normal cells. Although he was aware of the description by Tyzzer[34] of somewhat similar intranuclear bodies in the cutaneous lesions of varicella, Goodpasture did not associate the occurrence of the "protozoan-like cells" in the tissues of infants with viral infection. He regarded the lesion as a type of cytomorphosis. He stated that "their presence hardly indicates a disease entity, but rather they seem to represent an effect of chronic inflammation upon certain cells which may not be so stable in infancy as in adult life." He suggested that the cellular condition be identified by a descriptive name —cytomegalia. Goodpasture also made the very significant statement, as true today as it was then, that "this cellular change is of such a characteristic nature that there is no difficulty in recognizing it when present."

These characteristic cellular changes (nuclear and cytoplasmic inclusion bodies) so accurately described by Goodpasture in 1921, are now recognized as giving almost conclusive evidence of the presence of a virus. It is true that

somewhat similar nuclear changes have been described in tissues damaged by a variety of toxic agents,[35, 36, 37] but these nonviral inclusions are of the type designated by Cowdry[42] as type A—nongranular and not associated with evidence of severe cellular damage. In "inclusion disease" granularity is noted, and there is evidence of definite cellular degeneration (Fig. 2).

If evidence of the viral nature of inclusion disease depended solely on the presence of these inclusions, there would still be room for a reasonable doubt. The collateral evidence obtained from a study of similar conditions in guinea pigs,[38] hamsters,[32] mice,[40] and other rodents,[41] and in monkeys[42] is the final link in the chain of evidence which firmly establishes "inclusion disease" in humans as a viral infection. In these lower animals, entirely similar nuclear and cytoplasmic inclusions are constantly associated with the presence of a serially transmissible viral infection which under certain circumstances has fulminating lethal powers.[33, 40] As in humans, this viral infection is in lower animals, latent in salivary gland tissue, and whenever the salivary glands contain the inclusions they also contain the virus, which can be transmitted in series in animals of the same species (but not in animals of other species) by intracranial inoculation or by other routes. The constant association of the pathognomonic inclusions in lower animals with viral activity is as significant as is the association of intracellular acid-fast bacilli with rat leprosy. Neither human leprosy nor human inclusion disease has been transmitted experimentally, but both rat leprosy and rodent inclusion disease are readily transmissible, each within its own species. The reasons for regarding human inclusion disease as a viral infection are about as convincing as those for regarding human leprosy as a bacterial disease.

The failure to transmit human inclusion disease to experimental animals loses all value as an argument against the viral nature of the disease in the face of the above evidence from the field of comparative pathology. This failure can be readily explained on the basis of species specificity, which is known to exist among lower animals in inclusion disease, leprosy, bartonellosis, and many other infectious diseases.

There can be little doubt that the human virus could be isolated, with the formation of inclusions, outside of the human body if sufficient time were devoted to this problem—possibly in fertile eggs modified in their metabolism by methods known at present,[43] or perhaps in Maitland cultures containing human tissues. Success in this endeavor would furnish additional evidence in support of the view expressed above.

The salivary gland virus of the guinea pigs has been carefully studied cytologically and biologically by Rosenbusch and Lucas,[33] but its size has not as yet been determined.

PATHOLOGY

In the majority of previously reported cases, attention has been paid primarily to the inclusions, and the description of the associated pathologic changes

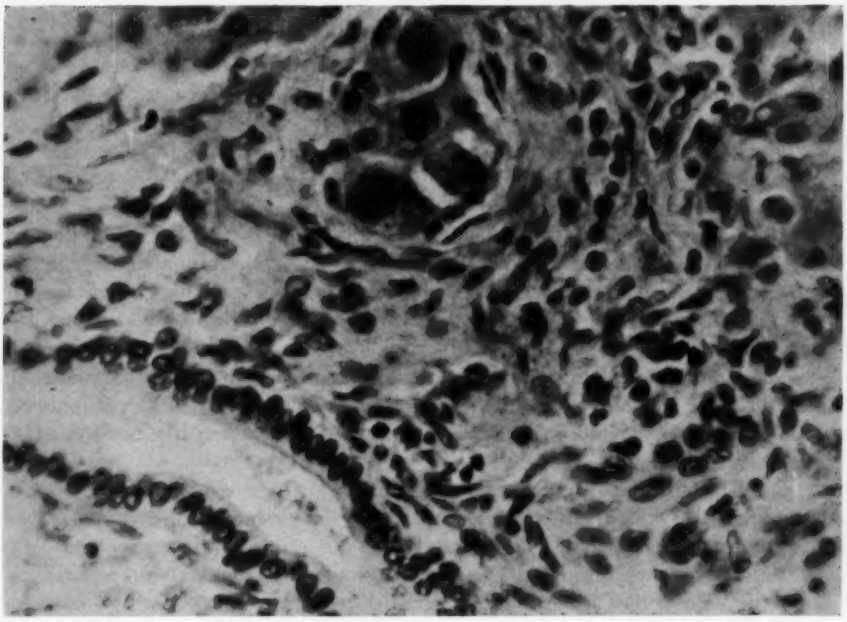

Fig. 5.—Liver showing inclusion bodies in bile duct cells. Periportal fibrosis with inflammatory cells. Case 6. Hematoxylin and eosin. (×400)

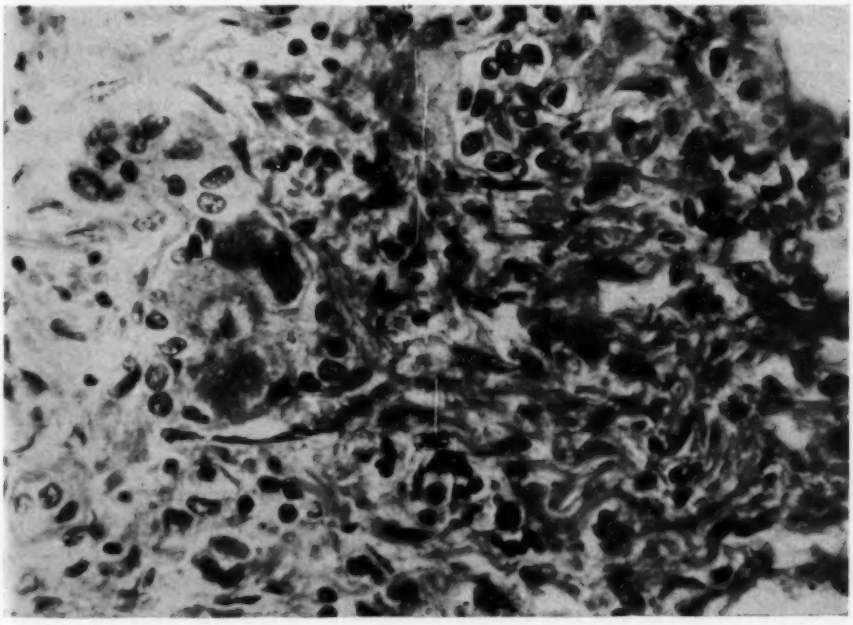

Fig. 6.—Decadent cells in the liver showing inclusion body debris. Fibrosis and hematopoietic cellular elements present. Case 6. Hematoxylin and eosin. (×540)

has usually been omitted or given only very briefly. For this reason, the pathologic picture will first be constructed on the basis of the six cases reported here, and then supplemented by such definite information as can be obtained from the preceding cases.

The outstanding pathologic change noted in all six of our cases was the presence of the inclusion-bearing cells. A detailed description of this cytological alteration has already been given. The inclusions varied in their visceral distribution, occurring in the lungs, adrenals, and kidneys in Case 1; lungs and kidneys in Case 2; in the lungs and liver in Case 3; in the lungs, kidneys, liver, brain, and adrenals in Case 4; in the lungs, pancreas, and kidneys in Case 5; and in the lungs, kidneys, liver, pancreas, thyroid, parathyroid, and salivary glands in Case 6. (The salivary glands were available for study only in Case 6.)

The number of inclusions found also varied greatly in the six patients, from the least involvement (not noticeable on casual low power examination) in Case 1 to the outstanding and intense involvement seen in Cases 4 and 6. (See Figs. 1 and 6.)

Many of the inclusion-bearing cells showed definite evidence of degeneration and irreversible necrosis. Inflammatory cell reaction to such degenerating cells was variable, but usually well marked.

Liver.—In two infants (Cases 5 and 6) severe structural alterations undoubtedly caused by the viral infection were present. There was moderate infiltration of lymphocytes and macrophages around the degenerating inclusion-bearing cells, but the most conspicuous response was a productive fibrosis. In Case 5 the resulting picture was that of early portal cirrhosis, while in Case 6 the appearance was more that of obstructive biliary cirrhosis. It is interesting to note that in spite of the marked liver damage in Case 5, inclusions were not particularly numerous (only one or two per low-power field).

Lungs.—The cellular reaction here was mainly mononuclear, and seen chiefly in the alveolar walls, so that interstitial pneumonitis of the type commonly seen in viral infections was present. All six of our patients showed this lesion, but it was most severe in one patient (Case 2), in whom the radiologic picture was considered suggestive of lipoid pneumonia. Only in one patient (Case 5) was there evidence of bacterial pneumonia.

Kidneys.—Five of the six patients showed inclusions in the kidneys. The involvement was variable in degree. In one patient (Case 4) about 25 per cent of all tubular epithelial cells were involved, and the pathologic diagnosis of severe nephrosis was obviously justified. This infant clinically showed elevation of the nonprotein nitrogen. Inflammatory reaction in the kidneys was of moderate degree, probably because the damaged cells desquamate rapidly and are removed in the urine.

Brain.—Involvement of the brain was pronounced in Case 4 and minimal in Case 5. In Case 4, necrosis of the inclusion-bearing cells, the scavenger microglial reaction, and the subependymal reparative astrocytic response, were all intense.

Intestine.—The ulcerative lesions in the ileum were attributable to the viral inclusion cells and responsible for the diarrhea, blood, and mucus.

Involvement of the *adrenals, pancreas, thyroid, parathyroid,* and *salivary glands* was probably not sufficiently extensive in any of our subjects to cause serious functional disturbance.

Miscellaneous lesions to be noted were extramedullary hematopoiesis (chiefly in the liver) in five patients, jaundice (Cases 5 and 6), ascites (Case 5), hepatosplenomegaly (Cases 4, 5, and 6), atelectasis (Case 1), edema of the glottis (Case 3), myeloid hyperplasia of the bone marrow (Case 6), and a maculopapular rash (Case 2).

The pathologic lesions may be summarized by the statement that there is a variable but on the whole a widespread visceral involvement with a necrotizing viral infection, and that the most conspicuous damage is usually found in the kidneys, liver, and lungs.

A study of the previously reported cases somewhat broadens the pathologic picture of the disease as described above. It is difficult to decide upon the role of the viral infection in causing some of the lesions described. Ulcerative colitis of viral etiology was apparently present in one adult case,[4] while one of the infantile cases shows ulcerative colitis the etiology of which is not clear.[1] Hydrocephalus (one case), cerebral hemorrhage (one case), and pancreatic fibrosis (two cases) are also difficult to evaluate. In view of our finding of involvement of the ventricular walls, one might hazard a guess that the hydrocephalus in the case reported by Müller[21] was part of the picture of the disease. The frequent recording of erythroblastosis, jaundice, and chronic pneumonia, as well as the frequent appearance of obvious nephrosis in the illustrations (even though not stressed in the texts) suggest that the pathologic lesions in past cases may have been, in general, similar to those in our cases. Several cases reported previously have been similar to Case 1 of our series in that there was little organic change to be seen other than the presence of occasional inclusions in the viscera.

CLINICAL PATHOLOGY

The laboratory study of our six patients was obviously incomplete. The positive hematological findings of interest were: in Case 4, the presence of severe anemia with relatively few erythroblasts in the peripheral blood smear; in Case 6, the presence of a few erythroblasts and normoblasts in the absence of an anemia; and in Cases 4, 5, and 6, the profound depression of the platelet counts throughout the entire course of the fatal illnesses. The elevation of the nonprotein nitrogen in Case 4 was indicative of some renal insufficiency. The van den Bergh reaction in Cases 5 and 6 was bimorphic, indicating liver damage, whereas an indirect response would have been present in early uncomplicated cases of hemolytic disease. Liver damage was further emphasized by the low plasma protein reading, the altered albumin-globulin ratio, increased prothrombin time, abnormal cephalin flocculation test, and bilirubin in the urine. Other biochemical and hematological results carried out in these cases were not of diagnostic significance. In the future, antigen and antibody studies of the Rh factor would be of value as well as routine serum investigations for syphilis.

CAUSE OF DEATH

It will be noted that the lesions found at autopsy in these six subjects (with the exception of atelectasis in Case 1) are all attributable to the activity of the virus. In Case 4 the massive involvement of the kidney was the probable cause of death while in Cases 5 and 6, although renal damage may have been a factor, the viral hepatitis was of sufficient degree to have caused death from disturbance of liver function. One patient (Case 3) died from respiratory failure, and a severe viral pneumonitis was present, but since a diagnosis of whooping cough was made this case may not represent an uncomplicated viral fatality. In Case 2 death also occurred from respiratory failure, and pathologically the only adequate cause of death found was the viral pneumonitis. Since the patient (Case 1) was stillborn, the cause of death is doubtful, but could well have been the viral infection. In one of the two cases described in adults,[5] it may be noted that the only important lesion found was a necrotizing interstitial pneumonia which in view of the huge number of inclusion-containing cells was quite clearly of viral origin.

This concept of the cause of death in inclusion disease is quite at variance with the previously expressed beliefs that the inclusions are incidental findings in infants dying of various causes, that they are an affect of chronic inflammation,[18] that they are not characteristic of any disease entity, and that no distinctive pathologic changes are found.[2] Our studies have also led us to believe that the virus is not saprophytic, as some workers have thought, but is rather to be characterized as necrotizing and lethal.

In previously reported cases, the presence of the inclusions has often been the only pathologic change recorded. Even in such cases the possibility that death may have been due to viral toxemia is by no means ruled out. In minks dying in fatal outbreaks of distemper,[44] there often are no lesions other than the presence of the cytoplasmic and nuclear inclusions in apparently undamaged cells, and the inclusions occasionally are found only after long search.

Association with bacterial infection, particularly whooping cough, has been more common in the previously reported cases than in our series. One of our patients had whooping cough, however, and this persistent association with whooping cough seems to be a finding which has not been satisfactorily explained.

DIAGNOSIS

At present, clinical diagnosis is probably not possible. The diagnosis may be suspected on the basis of clinical and laboratory evidence of renal, hepatic, pulmonary damage or enteritis not explainable on other grounds. In the more recent cases, the possibility of clinical confusion of the disease with hemolytic disease of the newborn infant (erythroblastosis fetalis) has become evident. Although inclusion disease may give rise to jaundice, bleeding tendencies, and erythroblasts in the peripheral blood, there is no evidence that it is etiologically related to the blood group incompatibilities. The hematological picture and the existence of thrombopenic purpura are adverse to a diagnosis of erythroblastosis fetalis. Failure to demonstrate Rh antibodies in the mother's sera in Cases 1, 4, and 5, and the exclusion of immunization in Cappell's patients,[31] support this

conclusion. Furthermore, the obstetrical histories of all six mothers were not of the pattern usually associated with fatal hemolytic disease of the newborn infant.

Some of the earlier examples of this disease were classified as congenital syphilis principally on the basis of visceral erythroblastosis, renal, and pancreatic changes.[2] In the newborn infants suffering from inclusion disease, persistence or possibly even recall of embryonic blood formation was not uncommon in the liver and spleen. Extramedullary hematopoiesis is not a specific hallmark of syphilis; it is of frequent occurrence in severe disease of varied etiology, being interpreted as a compensatory effect of severe marrow damage. In the absence of a hemolytic anemia it might be the result of viral stimulation of cells endowed with myelopoietic potencies. The cellular foci in numerous viscera and the pancreatic fibrosis are now known to be nonspecific alterations. Finally, the blood Kahn reaction of all maternal and fetal sera examined was negative.

Despite the difficulty of clinical diagnosis, an attempt to diagnose the condition is mandatory. A laboratory test in which the agent could be demonstrated would be ideal. As the virus has not been propagated outside of the human body, such a specific test does not exist as yet. Lacking this, a laboratory maneuver which would uncover the effects of the agent would be of great value. It is recalled that the involvement of the kidney in this generalized viral disorder is very common, and perhaps almost constant. Histological studies of the kidney reveals widespread intra-lumenal shedding (Fig. 1) of the unique inclusion-bearing cells (Fig. 2). It follows therefore that the kidney, an organ more easily studied than most, would through cytological studies of the urine be a logical organ to investigate. Exfoliative cytological studies of the urine in suspected cases of generalized cytomegalic inclusion disease might offer a practical method of diagnosis to the pediatrician.

The distinctive features of the morphological diagnosis of this disease may be recapitulated here:

1. Occurrence of nuclear and cytoplasmic inclusions.

2. Specific cellular gigantism, with cells measuring up to 35 microns in diameter.

3. Nuclear inclusions, huge, granular, acidophilic, or metachromatic, usually single, never more than two in a single nucleus, and surrounded by a pale halo. Prominent margination of nuclear chromatin and often two distinct marginal polar bodies.

4. Cytoplasmic inclusions, numerous and frequently localized in one portion of the cell, basophilic, uniform in size (2 to 4 microns in diameter), and spherical in shape.

5. Marked polymorphism of affected cells and their nuclei, with inclusions following the irregular contour of the nuclei.

6. Location largely in epithelial structures such as bronchial epithelium, liver cells, bile duct cells, renal tubular epithelium, and less often in adrenal, gastrointestinal epithelium (apparently the most common location for adults), pancreas, thyroid, and parathyroid.

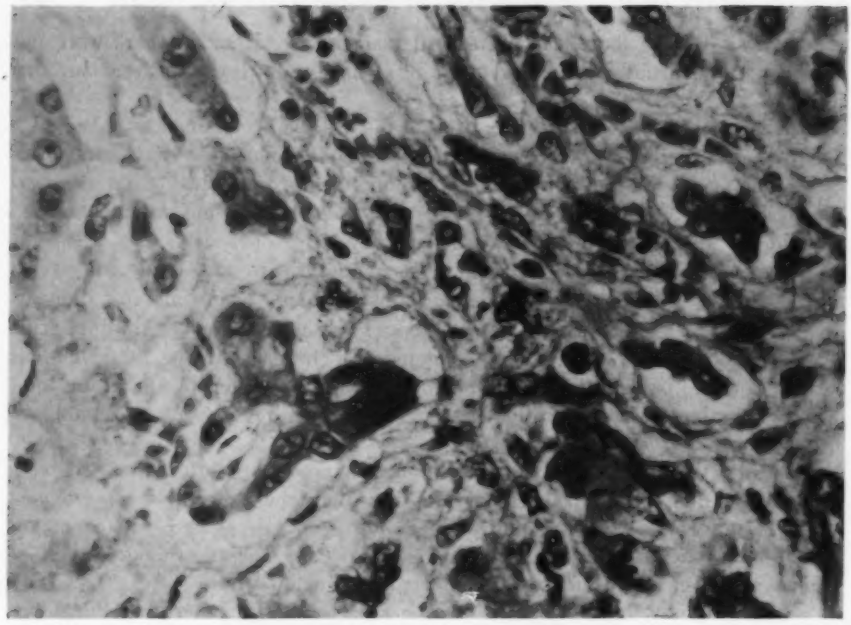

Fig. 7.—Liver with degenerating cytomegalic liver cell containing intranuclear inclusion. Liver cell degeneration and reparation also noted. Case 5. Hematoxylin and eosin. (×530)

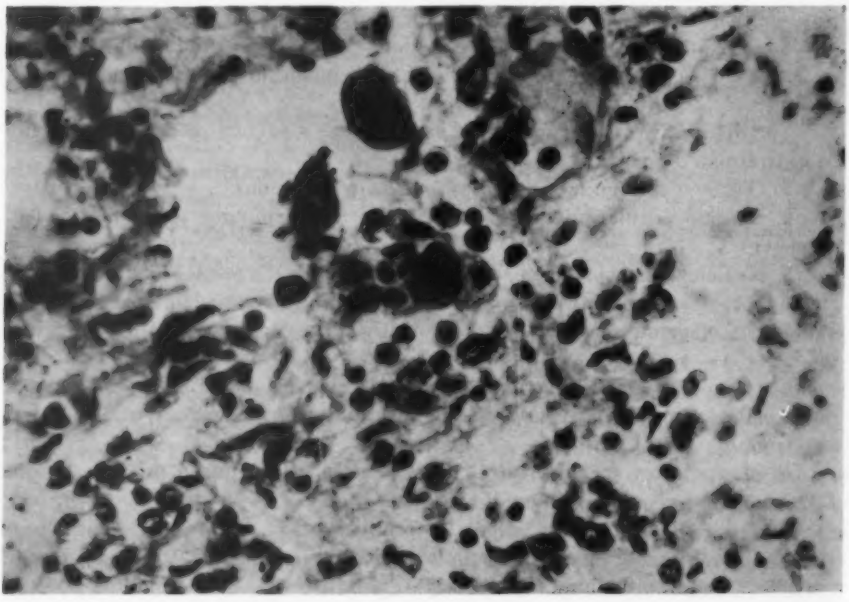

Fig. 8.—Lung. Interstitial pneumonia, cytomegaly, nuclear polymorphism and hypertrophy; all characteristic features of this disorder. Inflammatory cells intimately associated. Case 3. Hematoxylin and eosin. (×480)

Failure to find the cytoplasmic inclusions does not invalidate the diagnosis. In the analagous generalized infection produced experimentally in guinea pigs, the appearance of nuclear inclusions antedates the formation of cytoplasmic inclusions by seven to ten days. Cells containing cytoplasmic inclusions with normal nuclei are very rarely found. The occurrence of cytoplasmic inclusions in cells without visible nuclei (Fig. 4) is probably always the result of artefactual exclusion of the nucleus. The presence of inclusions within the nucleus and cytoplasm does not militate against a single virus being the incitant, as other viruses have stamped cells with both types of inclusions. The apparent occurrence of cytomegalia without either nuclear or cytoplasmic inclusions is rare and difficult to evaluate.

MORPHOLOGICAL DISTINCTION FROM OTHER DISEASES

As the lesions of cytomegalic inclusion disease are distinctive, it is possible to separate this condition from other inclusional entities. Chemically-induced inclusions can be eliminated as they are usually small, uniform in distribution, and intranuclear in situation. They retain the acid-fast tinctorial reactions,[45] and the affected cells lack the huge size and bizarre outlines so characteristic of inclusion disease. Finally, the coexistence of basophilic intracytoplasmic inclusions has not been reported in the experimental inclusions produced by heavy metals.[35, 36, 37] Basophilic cytoplasmic inclusions induced by stilbamidine in reticulo-endothelial cells are of an entirely different nature.[46] The cardinal features of cytomegalia and the presence of both nuclear and cytoplasmic inclusions serve also to separate this disease from the virus pneumonia described by Goodpasture and associates,[47] and the viral pneumonitis of Adams.[48] The absence of multinucleated giant cells and the large size of the nuclear inclusions clearly differentiate this disease from the giant cell pneumonia of Hecht.[49]

ACTIVATION OF THE VIRUS IN THE BODY

The existence of these inclusion bodies in the salivary glands in a high percentage of normal infants may be a visible manifestation of high local tissue immunity or dormancy of the virus. That viruses may remain in a dormant state has been known for many years. Certain conditions may alter the dormancy of the viral agent or change the receptivity of epithelial tissues for acceptance of the reawakened virus. Recently it has been demonstrated that anaphylactic shock can precipitate a herpes simplex encephalomyelitis, allowing the latent virus once again to express its virulence.[50] We have been unable to find evidence that repeated pregnancies, drugs, rubella infection, or prenatal immunizations have played an inciting or "conditioning" role for this smoldering virus. It has been suggested that acute suppurative processes, avitaminoses,[5, 51] whooping cough,[27] enteritis, or other debilitating disorders in infants may in some cases activate the virus or condition receptor epithelial structures. In the majority of reported cases however, no such activating agent has been apparent.

INTRAUTERINE INFECTION

That this condition can possibly have transplacental passage is indicated by the number of stillborn infants in which it is found. The effect of the virus may be more readily felt upon immature tissues. Arrest of development and tissue malformations such as choristial dysontogenesis associated with renal inclusions have been illustrated.[52] This affliction of the fetus suggests a mechanism of intrauterine infection similar to that believed to exist for other diseases such as toxoplasmosis and rubella. Under experimental conditions the animal salivary gland viruses can give rise to generalized lesions and this diffuse involvement is readily effected in the fetus.[53]

It would seem worthwhile to study embryos and young fetuses, which are usually neglected, for evidence of involvement with this viral infection.

PROGNOSIS

At present, only fatal cases of the infection are recognized, and little can be said about the possibility of recovery with or without residual organic damage. Such damage could not at present be ascribed to this viral infection in the absence of inclusions. On the basis of our morphologic evidence, the liver and brain both showed permanent damage. Two of the six cases presented patent histologic evidence of obstructive biliary and portal cirrhosis. The bile duct and liver parenchymal cells laden with disintegrating inclusions were found imprisoned in the sclerosing periportal zones (Figs. 6 and 7). One of the aftermaths of this disease may well be infantile cirrhosis.

The brain in one patient (Case 4) showed, in the subependymal regions, widespread cell necrosis, gliosis, and focal microglial response. These neuroglial responses are of an irreversible nature and could possibly produce obstructive intracranial disease.

NOMENCLATURE

The lack of uniformity in the nomenclature of this disease may have delayed its recognition as an entity. Many of the names used have been cumbersome or inappropriate. The simplest and perhaps most universally used term, "inclusion disease," is not sufficiently specific, since inclusions are associated with many diseases. We therefore suggest that an adaptation of the term "cytomegalia," originally used by Goodpasture[18] to indicate the bizarre cytological alteration characteristic of the disease to be incorporated into its name. The term "cytomegalic inclusion disease" seems to be descriptive and unlikely to cause confusion. Since this term may well be applied to the localized and dormant type of infection so common in the salivary glands, it seems necessary to refer to symptomatic or fatal cases as "generalized cytomegalic inclusion disease."

SUMMARY AND CONCLUSIONS

A study of six cases of inclusion disease (salivary gland virus infection) with a review of previously reported cases has led to the following conclusions, several of which are at variance with previously expressed concepts.

1. The etiological agent of the disease is a specific virus, which, per se, is a common cause of fetal and infantile death.

2. The morphology and cytology of the inclusion-bearing cells is pathognomonic of the disease.

3. The virus should be classed as necrotizing rather than saprophytic.

4. The clinical and pathologic pictures are variable, depending on the intensity of viral activity in different organs and tissues.

5. In uncomplicated cases, death may result from viral pneumonia, viral nephrosis, viral hepatitis, viral enteritis, and presumably from other mechanisms as yet undiscovered.

6. In cases of patients with visceral involvement but without associated pathologic changes, it is probably that death may result from viral toxemia.

7. In two patients, the viral hepatitis caused cirrhosis of the liver.

8. In one patient with a clinical picture of diarrhea, ulcerative enteritis associated with characteristic inclusions was found. This is the first instance in which infantile enteritis of viral etiology has been definitely established.

9. In two patients, inclusion-bearing cells were found in the brain in the subependymal regions. In one case the alterations were characteristic of a viral encephalitis.

10. Since the infection occurs during intrauterine life, it is suggested that it may be an unrecognized cause of fetal abnormalities and early fetal death.

11. Exfoliative cytological studies of the urine are suggested as a possible method for ante-mortem diagnosis, because of the frequent massive desquamation of inclusion-bearing cells into the renal tubules.

12. Investigation of this important disease by modern virological methods is urgently needed.

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STREPTOMYCIN AND PROMIZOLE COMBINED THERAPY IN TUBERCULOUS MENINGITIS IN CHILDREN

T. F. Su, M.D.,* and M. Y. Wu, M.D.†
Shanghai, China

STREPTOMYCIN alone sometimes will cure tuberculous meningitis, formerly a uniformly fatal disease.[1, 2] Fourteen patients with this condition in this hospital were given streptomycin alone; eleven died and three recovered.[3] However, Lincoln's results with combined streptomycin and Promizole were so much more promising,[4] that we treated sixteen patients with a slight modification of her regimen.

Patients.—From June, 1948, to April, 1949, thirty-two patients suffering from tuberculous meningitis were admitted to The Shanghai Public Hospital for Children. Sixteen of them were treated with combined streptomycin and Promizole, and six with streptomycin alone. The other ten were admitted too late in the course of the disease, died within one or two days of admission, or were discharged against advice soon after admission. Except for these drugs, all of these patients received the same treatment. Of the sixteen patients treated with streptomycin and Promizole, the three- to four-month course of combined therapy was completed in six; five were treated for more than two months, and five, who are not included in this series, were observed for less than one month.

On admission, in addition to a careful history, physical examination, and routine laboratory tests, the following procedures were carried out: x-ray film of chest, examination of the fundi, testing of the eighth nerve, tuberculin test (PPD), sedimentation rate (ESR), plasma cholesterol determination, and cerebrospinal fluid examinations, including cell count, differential count, sugar, protein, and chloride determinations, and a search for tubercle bacilli by smears, Löwenstein's culture medium, or animal inoculation. When the diagnosis had been established and treatment started, the above examinations and tests also were done daily or periodically as indicated.

Treatment.—Streptomycin was given intramuscularly (0.1 to 0.2 Gm., every four hours, according to the age and size of the patient, for from three to four months) and intrathecally (25 to 50 mg. daily for thirty days, and then every two days for sixty days). Also, from 1 to 1.5 Gm. of Promizole were given orally every day. It may be continued for from one to two years. In addition to the ordinary ward diets, extra nutrition, e.g., cow's milk, eggs, vitamins A, B_1, B_2, C, and D were added. Patients who could not take food by mouth were fed by nasal feedings and those who vomited frequently were given fluids parenterally and blood intravenously. As measles and whooping cough are the most serious complications of tuberculosis and may cause a relapse of tuberculous meningitis, adult blood and immune globulin were given to prevent

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*Physician-in-Chief, The Shanghai Public Hospital for Children, and Professor of Pediatrics, Tung Teh Medical College, Shanghai.
†Resident Physician, The Shanghai Public Hospital for Children.

measles, and three doses of diphtheria, tetanus, and pertussis combined toxoid and vaccine (DTP) were injected every four weeks during the course of combined therapy for the prevention of whooping cough.

Results.—The sixteen patients treated with streptomycin and Promizole are doing well. Up to the present, the six in whom the three- to four-month course of combined therapy was completed are symptom-free and without signs of relapse. The other five, who are still being treated, so far show definite improvement (Table I). Of the six control patients treated with streptomycin alone, two are improved (33.3 per cent), one is unimproved (16.6 per cent) and three died (50 per cent) (Table II).

TABLE I. DIAGNOSIS AND PROGNOSIS (COMBINED STREPTOMYCIN AND PROMIZOLE THERAPY)

CASE NO.	AGE IN MONTHS	SEX	DATE OF ADMISSION	CEREBROSPINAL FLUID		CHEST	DAY OF DISEASE (TREATMENT INSTITUTED)	PROGNOSIS†	DAYS OF OBSERVATION
				T.B.*	SUGAR (MG. %)				
1	7	M	June 3, 1948	+	Trace	Uppers	8	I	328
2	4½	M	July 7, 1948	+	Trace	Miliary	8	I	273
3	13	F	Aug. 22, 1948	+	Trace	Disseminated	2	I	253
4	36	M	Nov. 21, 1948	+	Trace	Left upper	3	I	162
5	30	F	Nov. 22, 1948	+	Trace	Right hilus	3	I	161
6	60	M	Jan. 8, 1949	+	Trace	Miliary	11	I	115
7	15	M	Jan. 14, 1949	+	20	Insignificant	8	I	109
8	48	M	Jan. 14, 1949	+	Trace	Right hilus	11	I	109
9	102	F	Feb. 3, 1949	+	40	Miliary	8	I	89
10	36	M	Feb. 8, 1949	+	60	Insignificant	3	I	64
11	30	M	Feb. 14, 1949	+	60	Uppers	4	I	78

*T.B. = Tubercle bacilli.
†I = Improved.

TABLE II. DIAGNOSIS AND PROGNOSIS (CONTROL CASES TREATED WITH STREPTOMYCIN ALONE)

CASE NO.	AGE IN MONTHS	SEX	DATE OF ADMISSION	CEREBRO-SPINAL FLUID		CHEST	DAY OF DISEASE (TREATMENT INSTITUTED)	PROGNOSIS†	DAYS OF OBSERVATION
				T.B.*	SUGAR (MG. %)				
1	5½	M	July 20, 1948	+	45		3	I	285
2	25	M	Sept. 26, 1948	+	20	Hilus and parenchymal	10	D	115
3	60	F	Oct. 5, 1948	+	35	Miliary	3	D	28th day of treatment
4	14	M	Nov. 26, 1948	+	Trace	Left upper	2	D	16th day of treatment
5	28	M	Dec. 6, 1948	+	8	Hilus	14	U-I	144
6	21	M	Dec. 10, 1948	+	Trace	Insignificant	3	I	133

*T.B. = Tubercle bacilli.
†I = Improved; U-I = Unimproved; D = Died.

In some of the sixteen patients given combined therapy, the delirium, abnormal mental status, fever, rigidity of the neck, and other neurological signs disappeared as early as the second or third week of treatment, while in others these signs remained until the second and third month. This difference in the duration of the signs may have been due to the physical condition of the patients, the extensiveness of their lesions, the time of starting treatment, and the presence or absence of toxic manifestations of the drugs.

After intrathecal injections of streptomycin, the cell count of the cerebrospinal fluid and the percentage of neutrophiles were usually increased, especially during the second to fourth weeks. The sugar content was low on admission in most of the patients and increased gradually during the course of therapy. Tubercle bacilli disappeared soon after treatment was started, except in two patients with miliary tuberculosis, in whom tubercle bacilli were found even at the end of the first month of therapy (Table III).

TABLE III. CEREBROSPINAL FLUID (COMBINED STREPTOMYCIN AND PROMIZOLE THERAPY)

CASE NO.	CEREBROSPINAL FLUID*	ON ADMISSION	END OF FIRST MONTH	END OF SECOND MONTH	END OF THIRD MONTH	LATEST	
							DATE
1	W.B.C.	42	350	150	120	21	Jan. 25, 1949
	Sugar	Trace	Trace	Trace			
	T.B.	+	+	0	0	0	
2	W.B.C.	62	350	150	50	0	Feb. 28, 1949
	Sugar	Trace	Trace	Trace	35	80	
	T.B.	+	+	0	0	0	
3	W.B.C.	21	680	80	36	8	Feb. 10, 1949
	Sugar	Trace	Trace	50	40	58	
	T.B.	+	0	0	0	0	
4	W.B.C.	504	900	340	200	10	April 15, 1949
	Sugar	Trace	30	68		75	
	T.B.	+	0	0	0	0	
5	W.B.C.	36	290	194	105	4	April 14, 1949
	Sugar	Trace			50	45	
	T.B.	+	0	0	0	0	
6	W.B.C.	80	100	62		30	April 3, 1949
	Sugar	Trace	55	45		30	
	T.B.	+	+	0		0	
7	W.B.C.	58	1,000	300	40		
	Sugar	20	65		45		
	T.B.	+	0	0	0		
8	W.B.C.	480	280	48	30		
	Sugar	Trace	65	55	50		
	T.B.	+	0	0	0		
9	W.B.C.	52	54	94			
	Sugar	40	35	25			
	T.B.	+	0	0			
10	W.B.C.	40	100	30	25		
	Sugar	60	60	45			
	T.B.	+	0	0	0		
11	W.B.C.	190	40	360			
	Sugar	60	50	35			
	T.B.	+	0	0			

*W.B.C. = white blood count per cubic millimeter; Sugar = mg. per cent; T.B. = tubercle bacilli.

The x-ray appearance of the lungs was improved in nine of the eleven patients by the end of the first month of treatment. No change was noted in the two patients with miliary tuberculosis (Table IV).

Toxic manifestations of streptomycin have occurred in most of the patients during the second to fourth weeks of treatment, characterized by increased irritability, increased cerebrospinal fluid cell count, skin rash, glossitis, overgrowth of hair, tremor, convulsions, and parkinsonianlike syndromes (Table V).

TABLE IV. X-RAY FINDINGS OF THE CHEST

CASE NO.	ON ADMISSION	END OF FIRST MONTH	END OF SECOND MONTH	END OF THIRD MONTH	LATEST
1	Right upper Left upper			Improved	
2	Miliary	Same	Improved	Improved	Almost well
3	Disseminated	Improved	Improved		No definite changes (March 9, 1949)
4	Left upper	Slightly improved	Resolution	Same	Further improved (April 5, 1949)
5	Right hilus			Same	Improved (April 4, 1949)
6	Miliary	Improved	Much improved		Further improved (April 4, 1949)
7	No important lesions				
8	Right hilus		Same		
9	Miliary	Film not satisfactory	Same		
10	No important changes				
11	Film too dark	Both uppers	Much improved		

TABLE V. TOXIC MANIFESTATIONS OF THE DRUGS (COMBINED STREPTOMYCIN AND PROMIZOLE THERAPY)

CASE NO.	1	2	3	4	5	6	7	8	9	10	11
Hypercholesterinemia	0	0	0	0	0	0	0	0	0	0	0
Sexual maturation	0	0	0	0	0	0	0	0	0	0	0
Thyroid enlargement	0	0	0	0	0	0	0	0	0	0	0
Leucopenia	0	0	0	0	0	0	0	0	0	0	0
Increase of cerebrospinal fluid cells	+	+	+	+++	+++	+	+	0	+	+	+
Symptoms of basal ganglia	0	0	0	0	+++	0	+	0	0	0	0
Convulsions	0	+	0	0	+	0	++	?	0	0	0
Tremor	0	+	0	0	++++	0	+	?	0	0	0
Blindness	0	0	0	0	0	0	0	0	0	0	0
Deafness	0	0	0	0	0	0	0	0	0	0	0
Nystagmus	0	0	0	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	0	0	0	0	0	0	0
Restlessness	0	+	+	++++	+	+	+	0	0	0	0
Hepatic disturbance	0	0	0	0	0	0	0	0	0	0	0
Renal irritation	0	0	0	0	0	0	0	0	0	0	0
Overgrowth of hair	0	0	0	0	++	0	++	+	0	0	0
Glossitis	0	0	0	+	0	0	++	0	0	+	0
Skin rash	0	+	0	++	++	+	++	0	+++	0	0
Fever	+	?	+	+	+	+	+	+	+	0	+
Irritation at site	0	0	0	0	0	0	0	0	0	0	0

COMMENT

Pharmacologic Basis of Combined Therapy.—The bacteriostatic action of streptomycin on tubercle bacilli accounts for the good clinical results in two of the six control cases of tuberculous meningitis treated with streptomycin alone. The chief drawback to streptomycin therapy is that in from three weeks to four months during the course of treatment, the tubercle bacilli may become resistant to the drug,[5] possibly due to the multiplication of a few resistant bacilli,[2] or to the mutation of the originally sensitive ones.[6] Consequently, patients with tuberculous meningitis who apparently have been successfully

treated with streptomycin may later have fatal relapses. Promizole (4,2′-Diaminophenyl-5′-thiazole sulfone) seems to have an inhibitory action on hematogenous tuberculosis.[7] Its toxicity is very low and it can, therefore, be administered for a prolonged period. The action of this drug, however, is usually delayed until it has been given for several weeks. Lincoln tried Promizole alone on five cases of tuberculous meningitis; but owing to this delayed action, all ended fatally (from six to twenty-five days of treatment).[7]

When streptomycin and Promizole are used in combination, the results are remarkably favorable. According to Lincoln's preliminary report[4] (88 per cent improved) and the results in our series (100 per cent improved), it is evident that the combined therapy of streptomycin and promizole has exerted an action greater than might have been anticipated from a simple summation of effects. Cocchi and Pasquinucci[8] have suggested that Promizole in combined therapy prevents the tubercle bacilli from becoming resistant to streptomycin.

Dosage.—The dosage of streptomycin is still a disputed problem, but there is a growing tendency to use smaller doses.[9] The dosage used intramuscularly in our series is more or less the same as that used by Lincoln.[4] The intrathecal doses ranged from 25 to 50 mg. In one late case, 100 mg. were given on a few occasions at the beginning of the treatment. According to Alexander's experience,[10] daily intrathecal injections of over 50 mg. may cause functional disturbances of the eighth nerve. When a reaction occurs, the patient should be desensitized, the dosage reduced, and then gradually increased to the original. Usually the degree of reaction is in direct proportion to the size of the dose. The dosage of streptomycin employed, therefore, must be decided according to the degree of infection and the possibility of toxic reactions.

So far the dosage of Promizole is not well defined. The estimation of its efficacy by determining its blood level is unsatisfactory because a high percentage of the drug combines with the plasma protein. In our series, 100-120 mg. per kilogram of body weight were given daily. The results were fairly satisfactory. No toxic manifestations were observed, although Promizole may cause thyroid and breast enlargement, and an increase in pubic hair, as well as the ordinary manifestations of sulfone drugs.[11]

Toxic Manifestations of Streptomycin.—These are: irritation at the site of injection, anaphylactic reactions, renal irritation and dysfunction, hepatic disturbance, histaminelike reaction, damage to the eighth nerve and interference with its vestibular function,[5, 12] stomatitis,[13] glossitis,[14] and toxic encephalopathy.[15]

Our experience is similar to that of Pfuetze and Pyle, who stated: "With the present regimen, the potential toxicity of streptomycin is chiefly a matter of a patient's idiosynerasy or acquired sensitization to the drug. Reactions of sensitization usually appear after treatment for from one to three weeks, with manifestations of fever, nausea, cutaneous eruptions, pruritus, and eosinophilia. Temporary withdrawal of streptomycin is necessary for the abatement of reactions of any severity, but most patients will tolerate the drug after a rest period, particularly if desensitization is carried out."[9]

Nutrition.—This is a very important problem in chronic diseases with a prolonged course of treatment. In tuberculous meningitis treated with combined therapy, the symptoms of the disease itself, e.g., fever, vomiting, and unconsciousness, and the toxic reactions of the drugs, e.g., fever, poor appetite, insomnia, and even signs of encephalopathy, may last for from one to two months, and greatly influence the patient's nutrition and prognosis. In our series, the nasal feedings, parenteral fluids, and blood transfusions frequently given in the early stage of the disease, and the high caloric and well balanced diets emphasized during the convalescent stage, have been important factors in our results which have been more satisfactory than any previously reported.

SUMMARY

1. Sixteen patients with tuberculous meningitis have been treated with streptomycin and Promizole in The Shanghai Public Hospital for Children. Six of them have completed the course of combined therapy without symptoms and signs of relapse; five have received treatment for over two months, and five have not been observed long enough to include in this report.

2. Eight of the eleven reported patients were boys, and three were girls. Their ages varied from 4½ months to 8 years, 6 months.

3. These eleven patients were observed for 328, 273, 253, 162, 161, 115, 109, 109, 89, 84, and 78 days, respectively.

4. During this same period, six nonselected patients with tuberculous meningitis were treated with streptomycin alone, as controls. Two were improved, one unimproved, and three died.

5. In the combined therapy, the daily intramuscular dose of streptomycin varied from 0.6 to 1.2 Gm. for three months, and intrathecal doses given daily or every other day were 25 to 50 mg. for a total of sixty injections. From 1.0 to 1.5 Gm. of Promizole were administered daily by mouth, and may be continued for one to two years.

6. Good nutrition was emphasized.

7. There was no difficulty in controlling the disease in each case, but the toxic reactions to streptomycin, especially anaphylactoid reactions, were frequently encountered. Desensitization was the best means of diminishing these reactions.

CASE REPORTS

Case 1.—H. S. H., a boy aged 7 months, was admitted on June 3, 1948, with the chief complaints of fever and cough of one week's duration and five convulsions in the preceding three days. Physical examination on admission revealed a semicomatose baby with a stiff neck and positive Kernig's, Babinski's, Brudzinski's signs, and ankle clonus. An x-ray picture of the chest showed tuberculous lesions in the right upper and possibly also in the left upper lobe. The cerebrospinal fluid contained 42 cells per cubic millimeter (90 per cent lymphocytes), a trace of sugar, and tubercle bacilli. The sedimentation rate (ESR) was 43 mm. per hour. As soon as the diagnosis was established, 0.1 Gm.

streptomycin was given intramuscularly every four hours and 50 mg. intrathecally daily. Two months later administration of 1 Gm. Promizole daily by mouth was started.

He ran a very smooth course, except for a slight increase in the cerebrospinal fluid cell count and mild fever in the third and fourth week. He received 73.1 Gm. of streptomycin in 118 days, including 3.8 Gm. given intrathecally in sixty-eight injections. He was discharged in good condition after four and one-half months of streptomycin therapy and two and one-half months of combined treatment. He is receiving 1 Gm. of Promizole daily, and is being followed up periodically in the clinic.

CASE 2.—M. L. C., a boy aged 4½ months, was admitted on July 27, 1948, after repeated attacks of cyanosis and dyspnea for twenty-four hours. An x-ray picture of the chest revealed miliary tuberculosis. Streptomycin was given intramuscularly in 0.1 Gm. doses every four hours. The cyanosis was slightly improved in three days. Ten days after admission, meningeal signs occurred. Lumbar punctures revealed an increase of cells in the cerebrospinal fluid. Tubercle bacilli were not found by smears but an animal inoculation was positive on Nov. 20, 1948. Daily intrathecal injections of streptomycin (50 mg.) were started on August 12. The chest condition and cerebrospinal fluid findings showed no improvement after one month of treatment. Toxic manifestations, i.e., fever, increase of cells in cerebrospinal fluid, and convulsions were noticed. Promizole was started September 29 (1 Gm. daily by mouth). His condition has improved steadily since. Urticaria and convulsions appeared again on October 20. Streptomycin therapy was discontinued. He had received a total of 47.7 Gm. of streptomycin in seventy-seven days, including 2.8 Gm. given intrathecally in fifty-seven doses. He was discharged on November 6, in good condition. He is now receiving 1 Gm. of Promizole daily, and has been followed periodically.

CASE 3.—L. L. K., a girl 13 months of age, was admitted on Aug. 22, 1948, for convulsions and meningeal signs for twenty-four hours. An x-ray of the chest revealed disseminated tuberculosis. The cerebrospinal fluid contained 21 cells per centimeter, tubercle bacilli, and a trace of sugar. The sedimentation rate (ESR) was 58 mm. per hour. Combined therapy was started the day following admission. Her condition improved steadily. Except for mild restlessness and an increased cell count in the cerebrospinal fluid during the fourth and fifth weeks of the treatment, no toxic reactions were observed. She received 86 Gm. of streptomycin in ninety-eight days, including 2.5 Gm. given intrathecally in fifty doses. She was discharged on November 29 in good condition. She is still receiving 1 Gm. of Promizole daily, and is being followed in the clinic.

CASE 4.—C. C. L., a boy 3 years of age, was admitted on Nov. 21, 1948, for drowsiness of two days' duration. An x-ray of the chest revealed hilar tuberculosis and infiltration of the left middle lobe. The cerebrospinal fluid contained

504 cells per cubic millimeter with 97 per cent lymphocytes, a trace of sugar, and tubercle bacilli. The sedimentation rate (ESR) was 20 mm. per hour. His mental status was clear after one week of combined therapy. Four weeks later, fever, an erythematous lesion on his face, and restlessness were noted. The cerebrospinal fluid cells had increased to 2,000 per cubic millimeter. These reactions abated when streptomycin was discontinued for one week, but recurred when the therapy was resumed. Glossitis was also observed later. Desensitization was carried out and the dosage of streptomycin was reduced. The child then steadily improved. He received 66.4 Gm. of streptomycin in ninety-four days, including 2.9 Gm. given intrathecally in sixty doses. The plasma cholesterol determination on February 28 was 220 mg. per cent, so 80 mg. of thyroid extract were given daily to prevent thyroid hypofunction. The patient was discharged on April 16, 1949, in excellent condition. He is still receiving 1.5 Gm. of Promizole daily, and is being followed up in the clinic periodically.

CASE 5.—C. K. W., a girl aged 2 years, 6 months, was admitted on Nov. 22, 1948, for convulsions of three days' duration. The child was drowsy on admission; her neck was stiff, and her extremities were spastic. An x-ray picture of the chest revealed hilar tuberculosis of the right side. The cerebrospinal fluid contained 36 cells per centimeter, a trace of sugar, and tubercle bacilli. The child became mentally clear after about four days of combined therapy. Ten days later fever (38° C.) was noted, followed in another ten days by an erythematous lesion, overgrowth of hair and vomiting. A coarse tremor of the left upper extremity was noticed on December 20, and of the right upper on December 24. Profuse sweating, flushing of the face, unconsciousness, spasm and jerking of the whole body, and "mask face" were noticed on December 30. Fundoscopic examination revealed a mild degree of congestion. She was given 100 c.c. of whole blood intravenously and 500 c.c. of saline subcutaneously on December 31. The blood transfusion was repeated on Jan. 6, 1949. Her condition was slightly relieved but not entirely free until one month later. Desensitization was done on January 15, and the dosage of streptomycin was temporarily reduced. Her condition steadily improved. She was discharged on April 15, in good condition. There were no residual signs of disturbance of the basal ganglia. She was able to talk and to answer questions readily. She received 69.66 Gm. of streptomycin in ninety-four days, including 2.05 Gm. given intrathecally in sixty doses, and is still receiving 1.5 Gm. of Promizole daily. She is being followed periodically in the clinic. As the plasma cholesterol was 238 mg. per cent before discharge, 80 mg. of thyroid extract has been given daily to prevent hypothyroidism.

CASE 6.—L. K., a boy 5 years of age, was admitted on Jan. 8, 1949, for vomiting and tremor of the extremities for three days. Two years previously the child had cervical lymphadenitis and x-ray evidence of pulmonary tuberculosis. On admission the child was dull, his cervical lymph nodes were enlarged, and his neck was stiff. An x-ray picture of the chest showed miliary tuberculosis. The cerebrospinal fluid contained 80 cells per cubic millimeter with 76

per cent lymphocytes, a trace of sugar, and tubercle bacilli. The sedimentation rate (ESR) was 5 mm. per hour. Combined therapy was started the day after admission. The boy complained of headache and vomited a few times three weeks later, and the cells in the cerebrospinal fluid increased to 200 per cubic millimeter. These symptoms and signs were relieved by oral Benadryl. The chest findings were unchanged and tubercle bacilli were found again in the cerebrospinal fluid at the end of the first month, but otherwise the child's condition improved. Urticaria occurred on February 2. He received 93.2 Gm. of streptomycin in 101 days, including 2.4 Gm. given intrathecally in sixty doses. He was discharged on April 13, in good condition. He is followed in the clinic periodically, and is still receiving 1.5 Gm. of Promizole daily.

CASE 7.—C. Y. T., a boy aged 15 months, was admitted on Jan. 14, 1949, with the chief complaint of fever and cough for one month following measles, and drowsiness for one week. An x-ray of the chest revealed no important findings. The cerebrospinal fluid contained 58 cells per centimeter, sugar 20 mg. per cent, and tubercle bacilli. Combined therapy repeatedly caused various toxic reactions, e.g., fever, vomiting, skin eruptions, overgrowth of hair, glossitis, insomnia, flushing of the face, marked sweating, tremor, and convulsions. Streptomycin was stopped and desensitization was carried out several times. However, the chest condition and the cerebrospinal fluid findings have definitely improved during his 108 days in the hospital. The course of combined therapy will be completed in another month.

CASE 8.—H. T. L., a boy 4 years of age, was admitted on Jan. 14, 1949, for headache, vomiting, and drowsiness for more than ten days. On admission he was unconscious, unable to cry, talk, or take food by mouth. An x-ray of the chest revealed right hilar tuberculosis. The cerebrospinal fluid contained 480 cells per cubic millimeter, and a trace of sugar. Tubercle bacilli were not seen in smears but an animal inoculation was positive on March 3. Combined therapy was started on admission. He was given nasal feedings for two months, and gained weight during the second month. After the second month he was able to take food by mouth, open his eyes, and to cry. Except for an overgrowth of hair, he had no toxic reactions.

CASE 9.—W. T. W., a girl, 8 years, 6 months of age, was admitted on Feb. 3, 1949, for fever, cough, and headache for three weeks, and drowsiness for one week. She was unconscious on admission. An x-ray picture of the chest revealed miliary tuberculosis. Tubercles were seen in the fundi of both eyes. The cerebrospinal fluid contained 52 cells per cubic millimeter, tubercle bacilli, and 40 mg. per cent of sugar. Streptomycin was given intramuscularly and intrathecally as soon as the diagnosis was established. Two days later urticaria occurred over the whole body, which was relieved by Adrenalin, and a reduced dosage of streptomycin. After one week of combined therapy, she became mentally alert, but the chest film did not show much improvement at the end of the second month. The combined therapy will be continued for another month.

CASE 10.—F. Y. C., a boy aged 3 years, was admitted on Feb. 8, 1949, for vomiting for two days, and convulsions for one day. His mother had died recently from advanced pulmonary tuberculosis. The patient was mentally clear on admission and had no abnormal neurological findings. An x-ray of the chest revealed no definite lesions. The cerebrospinal fluid contained 40 cells per cubic millimeter, tubercle bacilli, and 60 mg. per cent of sugar. Combined therapy was started on admission. Two weeks later measles occurred but the course of the tuberculosis was not changed. Aside from an increase in cerebrospinal fluid cells and mild glossitis, there were no toxic manifestations. He will receive another month of combined therapy.

CASE 11.—C. S. C., a boy, 2 years, 6 months old, was admitted on Feb. 14, 1949, for general malaise, repeated vomiting, and drowsiness for four days. An x-ray of the chest revealed tuberculosis of the hilus and both upper lobes. The cerebrospinal fluid contained 60 cells per cubic millimeter, tubercle bacilli, and 60 mg. per cent of sugar. Combined therapy was started after admission. Ten days later, measles occurred but the course of the tuberculosis was not altered. The only toxic reaction to streptomycin was an increased cerebrospinal fluid cell count in April. He is being continued on the streptomycin and Promizole therapy.

The authors wish to express their thanks to Dr. W. S. Fu and Dr. C. Sung for their kind permission to include cases in their services into this report. The authors are also deeply indebted to all resident physicians in this hospital for their faithful cooperation in carefully carrying out both diagnostic and therapeutic procedures. Thanks are also due to Drs. T. S. Jung and C. S. Tang for their kindness in making x-ray, fundi, and eighth nerve function examinations in this series of cases. Lastly, the cooperation of the Pasteur Institute in bacteriological and biochemical studies is also highly appreciated.

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ROCKY MOUNTAIN SPOTTED FEVER TREATED WITH CHLORAMPHENICOL AND AUREOMYCIN

WILLIAM A. REILLY, M.D., AND A. M. EARLE, M.D.
LITTLE ROCK, ARK.

SMADEL and associates[1, 2, 3] demonstrated the effectiveness of chloramphenicol (Chloromycetin) in experimental rickettsial and viral infections, and later treated twenty-five cases of scrub typhus and seven cases of epidemic typhus fever successfully with Chloromycetin. Pincoffs and associates[4] treated fifteen cases, and Carson and associates[5] treated two cases of Rocky Mountain spotted fever with Chloromycetin; none had any untoward effects.

A summary of six cases of rickettsial diseases diagnosed clinically as Rocky Mountain spotted fever (R. M. S. F., abbreviation hereafter used) are presented.

COMMENTS

The differential diagnosis of rickettsial diseases at times is difficult; this is especially so between epidemic typhus fever and R. M. S. F. However, with a detailed history and minute observation of the patient it is relatively easier. All of our patients gave a definite history of tick bite and came from a part of the country where R. M. S. F. is known to be present. The onset of the disease was within the range of the incubation period of three to fourteen days. All had negative stool, blood, and urine cultures for typhoid and negative agglutinations for tularemia, typhoid, paratyphoid, and brucellosis, except one patient (Case 3) who was known to have received typhoid injections one year prior to onset of present illness and whose agglutination for typhoid H was 1:80 on the third day of illness. The rash, in all cases, appeared from the second to sixth day; the lesions were maculopapular, either bright or dark red, and in all except one patient acquired a petechial character. The spleens were palpable in all cases and five patients had palpable livers; however, none showel clinical jaundice. There was some degree of mental involvement from dullness, stupor, and coma to restlessness, insomnia, delirium, muscular rigidity, and tremor in all of the patients.

Four patients out of the six had positive agglutination for 0 X 19. Specific compliment fixation test for rickettsial diseases was done through the courtesy of the United States Public Health Service Immunology Laboratory at Chamblee, Georgia. Although Case 2 had negative agglutinations for 0 X 19 on two occasions, we felt that clinically this was R. M. S. F. In case 5 the first agglutination was done on the third day of the disease and the patient was signed out by his father before a repeat could be obtained.

From the Department of Pediatrics, University of Arkansas School of Medicine, Little Rock. Journal Series No. 892.

TABLE I. SUMMARY OF CASES

CASE	NAME OR NO.	AGE	SEX	HISTORY OF TICK BITE	URINE, STOOL, BLOOD CULTURES	SPLEEN PALPABLE	JAUNDICE	TYPICAL RASH OF R.M.S.F.	AGGLUTINATIONS		COMPLIMENT FIXATION*		DAY OF DISEASE DRUG		DAYS UNTIL TEMP. NORMAL AFTER STARTING DRUG	TOTAL DOSAGE (GM.)	ANTIBIOTIC
									DAY OF DISEASE	O X 19	R.M.S.F.	RICKETTSIAL POX	STARTED	STOPPED			
1.	S. E.	2	F	Yes	Neg.	Yes	No	Yes	7	Neg.			8	13	3	2.0	Chloromycetin
									14	Neg.							
2.	G. W.	4	M	Yes	Neg.	Yes	No	Yes	7	1:40			5	13	3	9.5	Chloromycetin
									15	1:80	1:256	1:512					
3.	A. K.	15	M	Yes	Neg.	Yes	No	Yes	3	Neg.			4	10	6	18.0	Chloromycetin
4.	B. B.	4	F	Yes	Neg.	Yes	No	Yes	6	1:640			6	10	2		Chloromycetin
									10	1:1,280							
5.	R. D.	3½	M	Yes	Neg.	Yes	No	Yes	13	1:320	1:16	1:16	9	11	1	0.5	Aureomycin
									30	1:320			23	28		5.5	
6.	J. L.	16	M	Yes	Neg.	Yes	No	Yes	10	1:400			11	18	6	3.75	Aureomycin
									13	1:800							

*Courtesy United States Public Health Service.

In Cases 1 to 4, inclusive, treated with Chloromycetin, the drug was started on the sixth to eighth day of disease and continued for six to eight days. The temperature returned to normal in forty-eight to seventy-two hours after starting Chloromycetin in three patients and in one patient (Case 3) the temperature fell to 101° F. in seventy-two hours but remained elevated for the next forty-eight hours, after which it returned to normal. The dosage of Chloromycetin was 25 to 50 mg. per kilogram in twenty-four hours. In the two patients treated with aureomycin, one patient (Case 5) was treated at home by a local physician and was given 50 mg. of aureomycin five times a day for two days. The temperature returned to normal and the rash faded. The patient was admitted to a hospital three days later, and at this time he had no elevation of temperature or rash. He was observed without therapy for ten days when he had a sudden rise in temperature and a rash typical of R. M. S. F. reappeared. Aureomycin therapy was reinstituted, the temperature subsided after twenty-four hours, and the rash faded. The relapse was possibly due to too small a dosage of the drug initally. Case 6, also treated with aureomycin, was given an initial oral dose of 750 mg. by stomach tube and two subsequent doses of 250 mg. at four-hour intervals. After this the patient was given 60 mg. every four hours intramuscularly for seven days. There were no untoward reactions to either Chloromycetin or aureomycin.

In all cases the temperature ranged from 104° to 106° until institution of therapy, at which time the temperature began to decrease and the rash faded.

DISCUSSION

R. M. S. F. is a self-limited disease with an incubation period of three to fourteen days, an abrupt onset in severe cases with a sudden rise in temperature, moderate to severe headache, neurological manifestations, and generalized aching and pain in back, neck, and extremities. Vomiting may or may not be present. In milder cases the onset is more gradual. The characteristic rash of R. M. S. F. appears on the second to sixth day and may appear within twenty-four hours. The rash usually appears on the extremities first, but may appear on the trunk first as pointed out by Peterson and his associates.[6] The febrile period lasts from two to three weeks and the temperature falls by lysis by the end of the third week. The authors feel that their six patients conformed to this clinical course; however, antibody tests in two were negative.

SUMMARY

Six patients with rickettsial diseases with clinical findings and skin rashes typical of R. M. S. F. were successfully treated, four with Chloromycetin and two with aureomycin.

One patient (Case 5) suffered a relapse, possibly due to too small a dose of the drug initally, but responded on reinstitution of aureomycin.

The response to Chloromycetin in four patients and to aureomycin in one patient was in keeping with the findings of others.

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TYPHOID AND PARATYPHOID FEVER: A REVIEW OF FOUR CASES TREATED WITH CHLOROMYCETIN

McLemore Birdsong, M.D., Lieutenant Joe E. Mitchell, Medical Corps, United States Army, and William W. Waddell, Jr., M.D.
Charlottesville, Va.

DUE TO advances made in the field of public health and to the use of typhoid-paratyphoid vaccine, the incidence of typhoid and paratyphoid fever has been markedly reduced. However, when either occurs it is an illness of prolonged nature, leaving the patient weak and debilitated. Until fairly recently there was no specific treatment, with treatment being directed toward symptomatic and general supportive measures plus a high caloric, high protein diet.

Woodward and associates,[1] following the use of Chloromycetin in the treatment of scrub typhus, treated ten cases of proved typhoid occurring in the Malayan peninsula with Chloromycetin. The response in their patients was uniformly good, with the average duration of fever after the onset of therapy being three and one-half days. No severe toxic reactions to the drug were noted in their series of cases. Two of the ten patients developed relapse after ten and sixteen days, respectively. Both of these patients responded very well to a second course of Chloromycetin. Stiller[2] reported a single case of typhoid fever in which Chloromycetin was begun on the nineteenth day of the illness. Prior to the onset of therapy with Chloromycetin this patient's temperature had been spiking to 105° F. daily. After initiation of treatment with Chloromycetin the temperature dropped to 100° F. within sixteen hours and stayed below 100° F. throughout the remaining hospital stay.

The purpose of this paper is to report three cases of typhoid and one case of paratyphoid fever treated successfully with Chloromycetin.

Case 1.—C. T., a 6-year-old Negro boy, was admitted to the pediatric service of the University of Virginia Hospital on April 21, 1949, with a history of headache, fever, vomiting, nosebleed, progressive weakness, lethargy, and anorexia of ten days' duration. During this time he had had intermittent abdominal pain and diarrhea. Treatment elsewhere had consisted of penicillin and a sulfonamide with no response. Past history was noncontributory, but it was significant that the drinking water of the school which this child attended was downhill from an outdoor privy, and several cases of "intestinal flu" had occurred in other pupils.

Admission physical examination showed a very lethargic, chronically, and acutely ill child with marked abdominal distention. Temperature was 104.4° F. rectally, and his weight was 43½ pounds, with signs of recent weight loss. His hydration was poor. There was fresh hemorrhagic crusting bilaterally in the nose. The abdomen was symmetrically distended and tympanitic. There were a few inconstant expiratory dry râles heard throughout the chest. Deep tendon reflexes were hypoactive. The spleen was palpable one centimeter below the left costal border.

From the Department of Pediatrics of the University of Virginia Hospital.

Admission urine and lumbar puncture were negative. The hemoglobin determination was 11 Gm., with 4 million red blood cells and 7,350 white cells with 88 per cent polymorphonuclear cells. Two blood cultures were taken on admission and were later reported as negative. A stool culture was taken on admission and was later reported as positive for *Bacterium typhosum* by fermentation studies and agglutination of specific sera. Admission Widal test was negative, but one done ten days after admission was reported as positive at a titer of 1:80.

On the second hospital day the child was placed on Chloromycetin. He was given 25 mg. per kilogram of body weight every hour for three doses initially, followed by 250 mg. every three hours. On the day following institution of Chloromycetin his temperature, which had shown a daily spike to 105° F., went to a maximum of 102.4° F., and the child showed much less lethargy and was more alert. Forty-eight hours after onset of treatment with Chloromycetin, temperature reached a maximum of 100.2° F. and the patient appeared to be clinically well. After sixty-four hours of treatment the patient's temperature did not rise above 99.8° F. On the fifth day following institution of Chloromycetin the dose was cut in half, and nine days after treatment was started was discontinued altogether. (See Fig. 1.)

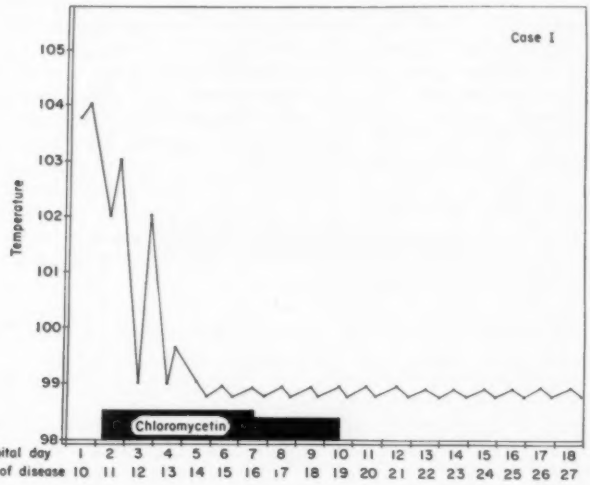

Fig. 1.—Chart showing response to Chloromycetin late in the course of the disease.

The patient was discharged from the hospital on the eighteenth hospital day, fourteen days after complete subsidence of all symptoms and eight days after Chloromycetin was discontinued.

He was seen in the outpatient department one week following discharge, at which time he was still doing well and weighed 46½ pounds, and he had been completely asymptomatic during the interim since discharge.

CASE 2.—B. B., a 9-year-old white girl, was admitted to the pediatric service on June 6, 1949, with the history of severe pain in the left side for two days prior to admission and of vomiting once. On the follow[illegible] day she had fever, headache, and continuation of her abdominal pain. [illegible] the morn-

ing of admission she had a large, foul, watery stool, following which she was given a cathartic by her mother. After this she began to have numerous watery, foul stools.

Except for a right hemiparesis and recurrent attacks of pyelonephritis, the past history was unimportant.

Admission physical examination revealed a well-developed 9-year-old girl appearing acutely ill and disoriented. Temperature was 102.6° F. rectally. Her right arm and right leg showed some atrophy, but reflexes could not be adequately evaluated at the time of admission. Her skin was hot and moderately dry. Her abdomen showed diffuse tenderness. There was moderate stiffness of the neck and bilateral positive Kernig's signs.

The admission laboratory studies showed the spinal fluid, catheterized urine, and serology to be negative. The hemoglobin determination was 11 Gm., with 4.03 million red blood cells, and 6,000 white blood cells, with smears showing 53 per cent bands, 7 per cent segmented, 35 per cent lymphocytes, and 35 per cent transitional monocytes with two early cells in the granulocytic series. Daily blood cultures were taken for three days. The first two were negative, and the third one was positive, being identified as *Bacterium paratyphosum B.* by fermentation and agglutination of specific sera.

In view of a past history of recurrent pyuria the child was started initially on streptomycin, in spite of the negative urine. Her temperature continued to spike between 102° and 104.5° F. daily on this regime, and she continued to be disoriented. Foul, watery stools increased in frequency. On the fourth hospital day, after the gram-negative, motile rods were found in the third blood culture, streptomycin was discontinued and the child was placed on 25 mg. Chloromycetin per kilogram of body weight every hour for three hours, followed then by 250 mg. every three hours. Twenty-four hours after onset of treatment with Chloromycetin the patient was clinically improved, and the temperature reached a maximum of 101.2° F. Her temperature dropped to normal sixty hours after treatment with Chloromycetin was begun, and remained normal during the next six hospital days. Five days after institution of Chloromycetin, the dose was cut in half and was maintained at 250 mg. every six hours for the next three days.

Repeated stool cultures taken from the day of admission through the sixteenth hospital day for a total of seven cultures were negative for paratyphoid and typhoid. Several urine cultures taken before and during treatment with Chloromycetin were negative for typhoid and paratyphoid. The Widal reaction did not become positive.

The rest of this patient's hospital course was complicated by two episodes of pyelonephritis due to *Bacterium coli*, which responded very well to sulfadiazine. On her twenty-first hospital day, following retrograde pyelograms, a left nephrotomy was done, and an aberrant artery blocking the left renal pelvis was divided and ligated, and a Foley-Y plastic operation was done. Following this the patient made an uneventful recovery and was discharged from the hospital.

CASE 3.—E. B., a 6-year-old Negro female child, was admitted to the pediatric service on Sept. 13, 1949, with the history of having had a high fever of three days' duration with abdominal pain. On the day prior to admission she had become very lethargic and on the day of admission had refused all food and liquid. Past history and family history were noncontributory.

Physical examination revealed a well-developed, well-nourished 6-year-old Negro girl who was very lethargic. Temperature was 105.6° F. rectally. Her skin was hot and dry. There was some vague abdominal tenderness and spasm in the right upper quadrant. The rest of the physical examination was essentially negative.

Admission stool and urine examinations were negative except for a 2 plus acetone and 1 plus albumin in the urine. Hemoglobin determination was 11 Gm., with 5.5 million red blood cells, and 14,000 white blood cells, with 70 per cent polymorphonuclear cells. A lumbar puncture done on the second day was negative. After three blood cultures were taken and a tentative diagnosis of typhoid fever made, the child was placed on 250 mg. Chloromycetin every four hours and 50,000 units of penicillin every three hours.

Penicillin was discontinued two days later when all three blood cultures were positive for *Bact. typhosum.* She improved symptomatically the first twenty-four hours and her temperature fell by lysis (see Fig. 2) and was normal four and one-half days after beginning treatment with Chloromycetin.

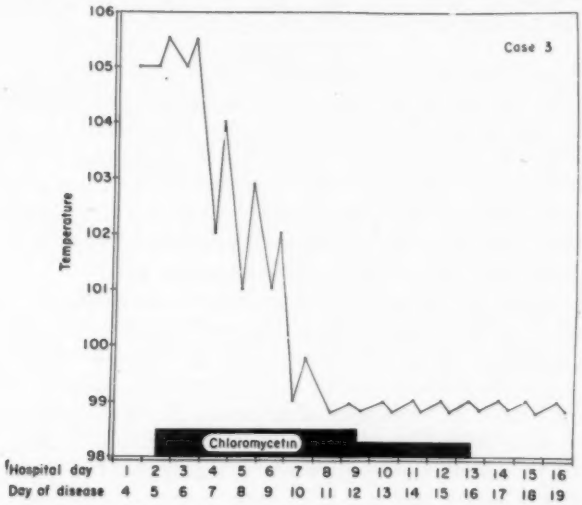

Fig. 2.—Chart showing response to Chloromycetin early in the course of the disease.

Following three days of normal temperature her dose of Chloromycetin was reduced by one-third for three more days. Then it was discontinued. She showed no more febrile episodes, and the rest of her hospital course was uneventful. Her Widal reaction was negative on admission and never became positive. Four stool cultures following subsidence of her fever were negative for typhoid, and she was discharged as well on the sixteenth hospital day, nine days after complete subsidence of her temperature. She was to return to the pediatric clinic for a one-week visit but failed to return. A report from a county health nurse was that she was doing well.

Case 4.—G. H., an 8-year-old Negro female child, was admitted to the pediatric service on Oct. 4, 1949, having had a high fever, diarrhea, and delirium of three days' duration. A sister living in the same house had had typhoid fever one month previously.

Physical examination on admission revealed a well-developed but malnourished, stuporous child with signs of moderate dehydration. Temperature was 105° F. rectally. There was diffuse abdominal tenderness. The rest of the physical examination was essentially negative.

Admission urine was negative. Hemoglobin was 13 Gm., with 4.45 million red blood cells, and 2,600 white blood cells with 53 per cent lymphocytes. Three blood cultures were taken, and the child was placed on 25 mg. of Chloro-

mycetin per kilogram of body weight every hour for three doses initially, followed by 250 mg. every three hours. All three blood cultures were later reported positive for *Bact. typhosum* by fermentation and agglutination tests.

Her temperature fell by lysis and was normal five days after the start of treatment. After five days of normal temperature the dose of Chloromycetin was reduced to one-half for six more days. She remained in a clouded mental state even after the temperature returned to normal.

The Widal reaction was initially positive at 1:80 for the "H" antigen but subsequently fell to 1:40 eleven days later when a rise should have occurred if treatment had been deferred. Several stool cultures before, during, and following treatment were all negative for typhoid.

Although showing clearing at the time of discharge on the twenty-second hospital day, the patient was still mentally clouded.

COMMENTS

The response in our three cases of typhoid and paratyphoid fever has been similar to that reported by Woodward and associates.[1] In the two cases of early typhoid, the fall in temperature was by lysis over a period of four and one-half to five days after institution of treatment. However, symptomatic improvement was noted in each case in twenty-four to forty-eight hours. The clearing of Case 4's mental state began during this time but then became static until after approximately ten days of normal temperature.

In the two cases of typhoid and one case of paratyphoid fever treated during the first week of illness, it is interesting to note that positive evidence of an immune reaction was not obtained by the Widal test. When the disease is allowed to run its natural course a rising titer is usually demonstrable against the "O" and "H" antigens of typhoid. It would seem likely that a patient treated early with Chloromycetin would be subject to early reinfection if reintroduced to material contaminated by the typhoid or paratyphoid bacilli, due to this possible lack of an immune response. Greater numbers of treated cases will be needed to prove or disprove this relationship.

It would appear from the prompt response which occurred with Stiller's one case, treated late in the disease, and from our Case 1, which was either in the late second or early third week of the disease, that the fall in temperature is more prompt, being almost by crisis. This is probably due to the immune response of the body which is beginning or present at this time, augmenting the effect of the drug.

Routine typhoid and paratyphoid vaccination is still rather widely practiced, especially in the South. Although vaccination has been very helpful in controlling these diseases, it is economically costly, and where there are reasonable public health facilities and supervision present the diseases occur only very sporadically, never in an epidemic form. Since it would now appear that a safe, efficient drug is available to shorten the course and ameliorate the symptoms of the diseases, we feel that there is a lesser need for the routine procedure of typhoid-paratyphoid vaccination, which in itself may cause distressing symptoms at times. However, in those few areas where the incidence of cases is very high, it would still seem advisable to carry out vaccination as a routine procedure.

SUMMARY

1. Three cases of typhoid and one case of paratyphoid fever treated with Chloromycetin are presented.

2. The immune response of the body is probably altered by early treatment with Chloromycetin.

3. With an effective therapeutic agent for treatment, the advisability of routine typhoid-paratyphoid vaccination, as used in many Southern communities, is questioned.

Since this report was sent to the publisher, another case of typhoid has been treated, and its response was practically identical to that of the ones presented.

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A STUDY OF THREE HUNDRED CASES OF DIARRHEA IN INFANTS AND CHILDREN DURING THE SUMMER AND FALL OF 1948

JULIAN D. LEVINSON, M.D., AND WILLIAM B. RAYCRAFT, M.D.
CHICAGO, ILL.

THE study of diarrhea in infants and children has received a new impetus from the recent investigations on the bacteriology of the stool and from the employment of newer therapeutic methods, particularly chemotherapy and antibiotics. One of the problems is the etiologic role of the proteus, paracolon, and pseudomonas groups. The efficacy of the chemotherapeutic and antibiotic agents is also an open question.

This prompted us to add some data obtained in a clinical and bacteriologic study of 300 cases of diarrhea in infants and children admitted to the Children's Division of the Cook County Hospital between June 1, and Nov. 1, 1948. We included in our series only severely ill patients who occupied hospital beds, and not the large number of infants and children with diarrhea who were treated on an outpatient basis.

Incidence.—The cases of diarrhea during the stated period constituted approximately one-sixth of the total hospital admissions. There was a steady rise of cases from June to a peak in September, and then a decline through October and November (Fig. 1).

Symptomatology.—(Table I.) Fever was present on admission in 284 patients or 94.6 per cent, with an average temperature of 103.2° F. rectally.

Diarrhea, although found in all our patients, was present at the time of admission in only 259 cases or 86.3 per cent. The remaining forty-one patients entered the hospital for some other complaint, and in twenty-four of these, the diarrhea did not manifest itself until at least twenty-four hours after the patient was in the hospital.

Vomiting was one of the presenting complaints in approximately one-half of the patients. When present, it was usually one of the initial symptoms, and stopped within twenty-four hours after admission.

History of abdominal pain or signs of tenderness was elicited in about 40 per cent of our patients.

Parenteral infection, most commonly upper respiratory infection or otitis media, was found in about one-fourth of the cases.

One of the most striking manifestations was the presence of neurological symptoms found in sixty-four patients, or 21.3 per cent.

Lethargy, present in thirty-seven cases, was the most common presenting complaint of the patients with neurological manifestations. Convulsions, usually of a generalized nature, were present in twenty-one cases. Fifteen patients complained of headache; eleven showed signs of nuchal rigidity; and six had positive Brudzinski's and Kernig's signs. Four patients were comatose on admission, four were delirious, two complained of vertigo, one showed extreme opistho-

From the Children's Division of the Cook County Hospital and the Hektoen Institute for Medical Research of the Cook County Hospital.
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tonos, and one each demonstrated ataxia and nystagmus. (Table II). It is interesting to note that in our series of cases, neurological symptoms were seen much more frequently in children over 2 years of age, despite the known greater susceptibility of the central nervous system in the younger age group.

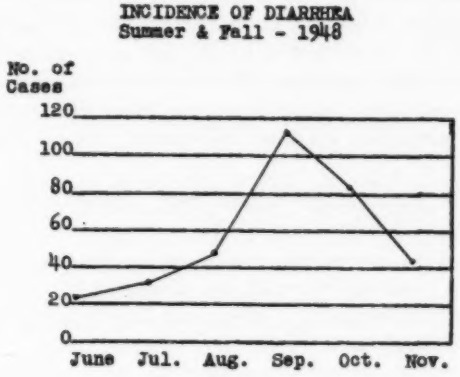

Fig. 1.

In seventeen patients the neurological manifestations were the initial symptoms, and the diagnosis of some acute central nervous system disease was made on admission. In fifteen of these patients, where lumbar puncture was performed, the cerebrospinal fluid was entirely normal.

It is easy to see how difficult the diagnosis may be where the neurological manifestations mask the diarrhea. It should be remembered, however, that it is possible to have a combination of diarrhea and acute central nervous system disease such as may occur in salmonella infection.*

Laboratory Studies.—The average white blood count on admission was 11,100 with a slight predominance of polymorphonuclear cells.

TABLE I. SYMPTOMATOLOGY ON ADMISSION

	NO. OF CASES	PER CENT OF TOTAL
Fever	284	94.6
Diarrhea	259	86.3
Vomiting	154	51.3
Abdominal pain or tenderness	122	40.6
Parenteral infection	69	23.0
Neurological	64	21.3

TABLE II. NEUROLOGICAL MANIFESTATIONS*

SYMPTOM	NO. CASES	SYMPTOM	NO. CASES
Lethargy	37	Coma	4
Convulsions	21	Delirium	4
Headache	15	Vertigo	2
Nuchal rigidity	11	Opisthotonos	1
Brudzinski's and Kernig's signs	6	Ataxia	1
		Nystagmus	1

*In seventeen cases neurological manifestations were the initial symptoms of the disease. Fifteen spinal taps revealed normal findings.

*Two cases of salmonella meningitis were observed in patients at our hospital after the present series was closed. One died and one recovered.

Blood cultures in 100 patients were negative except for nine cases in which beta-hemolytic staphylococcus was recovered and one which showed *Streptococcus viridans*. The urine was negative in all cases.

The stools were studied for bacteria, parasites, and virus. Microbiologic studies were carried out in the Department of Bacteriology of the Cook County Hospital. The stools were studied for bacteria by the following method: Rectal swabs were placed in tetrathionate broth and after twenty-four hours were streaked on Levine's eosin methylene blue, sodium azide, and shigella-salmonella (S.S.) plates. Twenty-four hours later, one more S.S. plate was inoculated. Further study of suspicious colonies was carried out according to established methods.[1]

In cases where parasitologic studies were carried out, zinc flotation and hematoxylin-stained slides were employed.[1]

Virus studies were carried out after treating the stools with penicillin and streptomycin. The resultant material was scratched into a rabbit's cornea, fed and inoculated intraperitoneally in mice, and injected intracerebrally in mice, rabbits, and guinea pigs.

Bacteriology of the Stool.—In seventy-eight cases, or 26 per cent, shigella was recovered and in seventeen cases, or 5.6 per cent, salmonella. Five patients had both shigella and salmonella on stool culture. In 124 cases, or 41.3 per cent, organisms of the proteus group, paracolon, or *Pseudomonas aeruginosa* were found in the stool cultures. In seventy-eight cases, or 26 per cent, only bacteria considered as parts of the normal flora of the intestinal tract were isolated.

Eight cultures, or 2.6 per cent, showed pathogenic or potentially pathogenic parasites. Four of these had *Endamoeba histolytica*; two had *Endamoeba coli*; and one each had *Endolimax nana* and *Giardia lamblia*. Parasitologic studies performed in sixty-six other cases of diarrhea and in 100 control cases were all negative.

Virus studies in thirty-two cases performed on rabbits, mice, and guinea pigs were all negative.

It will be noted that proteus, paracolon, and pseudomonas organisms occurred four times as frequently in patients under one year of age than over one year. Shigella, on the other hand, was found ten times more frequently in children over one year. Salmonella was found in about equal numbers. All the patients showing pathogenic parasites were over one year of age.* (Table III).

In an effort to determine the possible pathogenic role of proteus, paracolon, and pseudomonas, control studies were performed on ninety-two patients without diarrhea under one year of age, and on 250 patients over one year of age. *Escherichia coli* was found in 91 per cent of the controls, enterococci in 68 per cent, and *Aerobacter aerogenes* in 49 per cent. This was a higher incidence than that found in the diarrhea patients, and we therefore concluded that these organisms were not pathogenic in our cases. It should be pointed out, however, that even normal flora of the intestinal tract may become pathogenic under certain conditions.

*Shortly after our study was concluded, a case of amebiasis was observed in a 12-day-old premature infant. This infant died.

TABLE III. BACTERIOLOGY OF STOOL

ORGANISM	UNDER ONE YEAR OF AGE	OVER ONE YEAR OF AGE	TOTAL	PER CENT
Proteus, paracolon, and pseudomonas	100	24	124	41.3
Normal flora	55	23	78	26.0
Shigella	7	71*	78*	26.0
Salmonella	7	10*	17*	5.6
Parasites	0	8	8	2.6

*Includes five cases in which both shigella and salmonella were found.

In cases of diarrhea where no shigella, salmonella, or parasites were found, we compared the incidence of pseudomonas, proteus, and paracolon organisms to a corresponding group of controls. Under one year of age, only organisms of the proteus group alone occurred in a significantly higher percentage than in corresponding controls. Over one year of age, only paracolon organisms alone occurred in a much higher percentage (Table IV). We therefore concluded that the presence in the stool culture of protei in patients under one year of age, or of paracolon in patients over one year of age was of significance in our cases.

TABLE IV. COMPARATIVE BACTERIOLOGY OF DIARRHEA AND CONTROLS

ORGANISM	UNDER ONE YEAR OF AGE		OVER ONE YEAR OF AGE	
	PER CENT OF 92 CONTROLS	PER CENT OF 155 DIARRHEA CASES	PER CENT OF 250 CONTROLS	PER CENT OF 46 DIARRHEA CASES
Ps. aeruginosa alone	20.7	12.3	4.0	8.7
Proteus alone	13.0	38.0	6.4	10.8
Paracolon alone	9.8	6.5	6.8	26.0
Paracolon and protei	4.3	3.2	3.2	4.3
Protei and pseudomonas	4.3	2.6	2.0	0.0
Pseudomonas and paracolon	2.2	1.9	2.0	2.2
Paracolon, pseudomonas, and proteus	0.0	0.0	1.6	0.0

Mortality.—There were twenty-six total deaths or a total mortality rate of 8.6 per cent. Ten deaths occurred in the first twenty-four hours after admission, giving a corrected rate of 5.3 per cent. Twenty-three deaths were in patients under one year of age, including seven premature infants (Table V). Our mortality rates compare favorably with other series, in spite of the fact that our patients were, with few exceptions, severely ill.

TABLE V. MORTALITY

		MORTALITY RATE (%)
Total deaths	= 26*	8.6
Twenty-four hour deaths	= 10	
Over twenty-four hour deaths	= 16	5.3

*Twenty-three deaths under one year of age including seven premature infants.

Two fatal cases, both patients over 2 years of age, had shigella of Flexner type IV on stool culture, and two cases, patients under one year of age, had protei. In the other patients who died, only normal flora of the intestines were found.

Therapy.—Our patients received both general and antibiotic therapy. The general treatment consisted of starvation for from eight to twenty-four

hours except for tea, following which the patients were given either skimmed lactic acid milk or dilute evaporated milk. Most patients received Kaopectate, and about one-third of the patients received calcium lactate orally. Almost all of the patients in our series required parenteral fluid, the intravenous route being the one of choice in severely ill patients. Approximately 35 per cent were given blood or plasma.

The antibiotic treatment consisted of a five-day course of sulfadiazine, oral streptomycin, or a combination of the two. One grain per pound per day of sulfadiazine in divided doses, and 100,000 units of streptomycin every three hours were the dosages used.

Sixty-two patients with positive stool cultures for shigella were treated. Forty out of forty-six patients given sulfadiazine alone had negative stools after a course of therapy. In six of the seven who received oral streptomycin, the stools became sterile for shigella. A combination of the two therapeutic agents cleared up all of the nine cases in which it was used. Streptomycin proved effective in some sulfa-resistant cases and vice versa. While the number of patients treated was small, the drugs appeared of about equal efficacy; and a combination of the two was the most satisfactory treatment (Table VI). In vitro studies showed shigella organisms in most cases to be sensitive to a concentration of 12.5 units per cubic centimeter of streptomycin or less. Five patients, however, required 50 units per cubic centimeter of streptomycin for complete inhibition.

TABLE VI. THERAPY OF SHIGELLA

	NO. CASES	NEGATIVE STOOL CULTURES	PER CENT CURES
Sulfadiazine	46	40	87
Streptomycin (oral)	7	6	86
Sulfadiazine and streptomycin	9	9	100

TABLE VII. THERAPY OF DIARRHEA CAUSED BY ORGANISMS OTHER THAN SHIGELLA OR SALMONELLA

TREATMENT	AVERAGE DURATION OF DIARRHEA (DAYS)
Supportive therapy only	4.9
Supportive plus sulfadiazine or streptomycin	2.8

It was difficult to evaluate the effect of drug therapy by stool cultures on the other diarrheas. In patients who received sulfadiazine or oral streptomycin, the diarrhea stopped on an average of 2.8 days compared to 4.9 days for those receiving general treatment only (Table VII).

DISCUSSION

The role played by paracolon, proteus, and pseudomonas in the causation of diarrhea has not been definitely established. Stuart, Wheeler, Rustigian, and Zimmerman[2] reported an outbreak of gastroenteritis in which patients and food handlers showed the same strain of paracolon. Sandiford,[3] on the other hand, concluded that paracolon was not an etiologic agent in diarrhea. Felsenfeld

and Young,[4] in a survey of several hundred cases of diarrhea and controls in an adult population, showed a much higher incidence of proteus and paracolon in the patients with diarrhea than in the corresponding normal individuals. *Ps. aeruginosa* has been implicated in an isolated epidemic.[5] The conclusions we reached, namely, that protei were of pathogenic significance in our cases of diarrhea in patients under one year of age, and paracolon in those over one year, we feel are valid.

Recent literature contains a good deal of data on the use of certain therapeutic agents employed in the treatment of diarrhea. Finerman and Weiss,[6] in a study of 1,000 adult cases of shigella dysentery treated with sulfaguanidine showed this drug to be effective in doses of 10 Gm. a day for from seven to ten days. The work of Watts and Cummins[7] and Hardy[8] on a large series of cases showed that sulfadiazine was superior to other members of the sulfonamide group, both the absorbable and the nonabsorbable types.

A limited number of reports have appeared in the literature regarding treatment of diarrhea by the administration of streptomycin. The results of oral streptomycin therapy have been encouraging in the hands of some investigators.[9] Other authors, however, have not found streptomycin efficacious.[10, 11] The consensus of opinion regarding the route of administration of this drug is that the oral route is preferable to parenteral injection.[12] Our results justify our contention that both sulfadiazine and streptomycin are of value.

Our mortality figures compare favorably with those of other investigators. Weihl, Rappoport, and Dodd[13] showed a mortality of 7.5 per cent in a series in which about 62 per cent of their cases were classed as mild or moderate in severity. Premature infants were not included in this series. Alexander and Eiser[14] in 1944 had a mortality rate of 12 per cent in their severely ill patients. Gairdner[15] in a report of 215 cases from England had a mortality of 51 per cent.

As regards the therapeutic value of early intravenous therapy, including blood and plasma administration, we feel it has a definite value in reduction of mortality. This is in agreement with the observations of Glaser and Bruce[16] and Govan and Darrow.[17] The latter authors included intravenous administration of solutions containing potassium chloride in their regimen of treatment.

SUMMARY

1. A study is presented of 300 cases of diarrhea in patients admitted to the Children's Division of the Cook County Hospital in the five-month period beginning June 1, 1948. These comprised one-sixth of the total admissions with a peak of diarrhea cases in September.

2. The most common symptoms on admission were fever and diarrhea, although in many instances diarrhea did not develop until later.

3. Neurological manifestations were found in 21 per cent of the cases, and were more common in children over 2 years of age. Neurological symptoms were often so prominent as to mask the underlying disease. In all cases where spinal puncture was performed, the fluid was found to be normal.

4. In this epidemic, shigella was found in 28 per cent of the cases, salmonella in 5 per cent, and proteus-paracolon-pseudomonas organisms in 46 per cent. Shigella was found ten times more frequently in children over one year of age than in those under one year of age. The proteus-paracolon-pseudomonas organisms were found four times as frequently in children under one year of age.

Control studies showed that proteus organisms in patients under one year and paracolon in patients over one year of age were of pathogenic significance. Virus studies in thirty-two cases of diarrhea were negative.

5. The mortality rate was 8.6 per cent, with a corrected rate, excluding the twenty-four-hour deaths, of 5.3 per cent. Our mortality rate compares favorably with that of other series, in spite of the fact that our patients were, with few exceptions, severely ill.

6. In the therapy of shigella, sulfadiazine and oral streptomycin were found of about equal efficacy, with a combination of the two as most effective.

7. In diarrhea caused by organisms other than shigella or salmonella, it was found that the average duration of the diarrhea was cut from approximately five to three days by the use of either sulfadiazine or oral streptomycin.

8. We feel that a combination of the early use of intravenous fluids, including blood or plasma, the use of sulfadiazine and oral streptomycin, plus good nursing care, will tend to reduce the mortality and hasten the recovery in patients with diarrhea.

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NEPHROLITHIASIS AND NEPHROCALCINOSIS WITH CALCIUM OXALATE CRYSTALS IN KIDNEYS AND BONES

JOYCE S. DAVIS, M.D., DALLAS, TEXAS, W.G. KLINGBERG, M.D., ST. LOUIS, MO., AND ROBERT E. STOWELL, M.D., PH.D., KANSAS CITY, KAN.

CALCIFICATION of the renal parenchyma in infants has been frequently reported.[1, 2] In most instances it is associated with dehydration, acidosis, gastroenteritis, pyloric stenosis, or tetany. Older children with renal calcification usually have also had an associated dwarfism, rickets, and acidosis.[1, 3] In 1942, Wohl[4] reported the case of a normally developed 11-year-old boy with diffuse renal calcification who had no complaints and only slight impairment of renal function. This boy is now 18 years old, and recent studies present signs of progressive renal damage, acidosis, and a polycythemia.[5] Analysis of a stone passed following an attack of renal colic revealed calcium phosphate, oxalate, and carbonate. Stones from other patients, including adults, have usually consisted of carbonates and phosphates,[1, 6, 7] although a considerable percentage of oxalate stones has been reported.[8] Reports of diffuse and focal renal calcification in adults are most frequently associated with urinary tract infection or hyperparathyroidism.

The following case is reported because of the unusual character of the clinical course and the remarkable findings at autopsy.

CASE REPORT

J. M. was first admitted to the St. Louis Children's Hospital on Sept. 15, 1938, at 3 years of age. The chief complaints were those of intermittent fever for three months and sore throat intermittently all his life. The family history was noncontributory. The past history revealed that his general health had been poor. Frequent respiratory infections had resulted in poor feeding habits, so that he took little solid food, his diet consisting mainly of milk. Orange juice and cod liver oil were given intermittently. The developmental history was normal. The initial present illness revealed that in the past three months he had had frequent bouts of fever of from 103° to 104° F., lasting several days and associated with severe vomiting, which were usually diagnosed as acute tonsillitis. For the previous three to four months he had polydipsia and polyuria. In the past two to three weeks the urine was milky in appearance. Also, for about one month prior to admission, the patient, when voiding, would hold his abdomen as if in slight pain. He had been seen in the Washington University Clinics with frequent respiratory infections and tonsillitis.

Physical examination at that time revealed a rather poorly developed and poorly nourished white boy whose tonsils were quite large and cryptic but not inflamed. The anterior cervical lymph nodes were enlarged to a moderate

From the Departments of Pathology and Pediatrics, Washington University School of Medicine and St. Louis Children's Hospital, St. Louis, Mo.

degree and the rest of the physical examination was essentially negative. At no time were any masses palpable in the abdomen. The laboratory findings are summarized in Table I. The hemogram was essentially normal. Tuberculin and Kahn tests were negative. Repeated cultures of catheterized urine showed no growth. A flat film of the abdomen (Fig. 1) revealed numerous patchy areas of calcification on both sides opposite the first, second, and third lumbar vertebrae, and overlying the kidney shadows. These were fairly symmetrical and

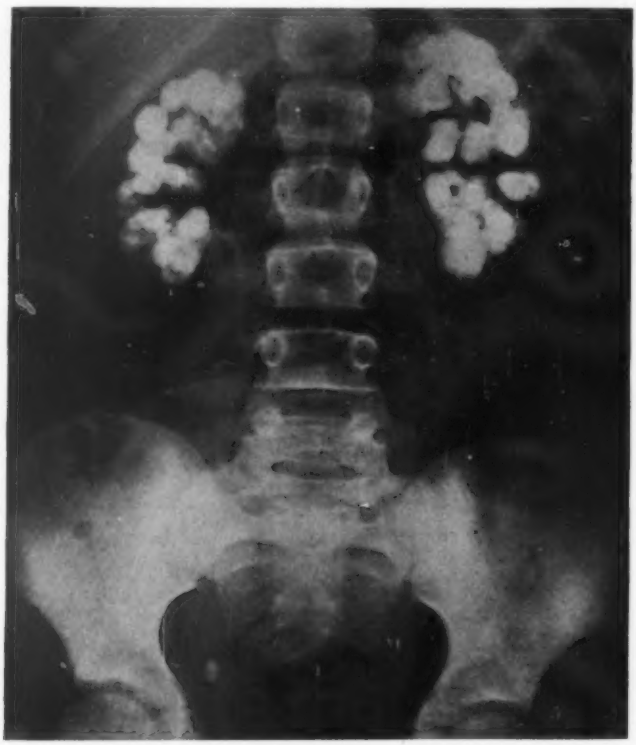

Fig. 1.—X-ray on fourteenth admission is typical of all taken since the first admission, with the exception of the stone in right ureter.

were thought to be "coral" kidney calculi bilaterally. Because of the continued low specific gravity, albuminuria, and the kidney calculi just described, further renal function tests were performed. (Table I.) Thus, on the first admission there was evidence of marked renal damage, at that time well compensated by polyuria and polydipsia. The amount of renal damage was not sufficient to cause a urinary retention of phosphates nor an elevation of the nonprotein nitrogen. An intravenous pyelogram did not show sufficient concentration of dye to be diagnostic. Roentgenograms of the long bones and skull were entirely

TABLE I. LABORATORY AND CLINICAL DATA

DATE	9/15/38	10/7/40	1/4/42	6/16/43	5/24/47	7/12/47	8/25/47	9/8/47
Blood								
Nonprotein nitrogen (in mg. per cent)	26	33	49	39.5-46	92	160	144	357
Total protein (in Gm. per cent)	8.11	6.54		7.55				
Albumin (in Gm. per cent)	4.98	4.32						
Globulin (in Gm. per cent)	3.13	2.22						
Calcium (in mg. per cent)	12.8	11.4		11.5	11.6	11.6	5.8	7.7
Phosphorus (in mg. per cent)	4.5	6.1		3.8	5.7	6.9	9.7	
Chloride (in mg. per cent) expressed as NaCl	603	590		595				
CO_2 combining power in volume (per cent)	40	58.5		60.5		35	44.5	
Urea clearance, first hour excretion (per cent)	81	—	—	47				
Urea clearance, second hour (per cent)	86	—	—	52				
Whole blood urea nitrogen (in mg. per cent)	17.5			26.8				
Urine								
Cultures	negative	one positive		negative	negative	negative		negative
Specific gravity	1.004	1.004-1.010	1.008			1.001-1.005	1.001	
pH	6.5							
Albumin	+		+		+			
White blood cells	many		many		occasional			
Blood Pressure	76/58	80-90/50-60	110/80				135-180/110-130	

normal. He was discharged from the hospital and followed in the outpatient department, receiving ammonium chloride in doses sufficient to maintain an acid urine, with the hope of dissolving the stones.

He was readmitted two months later on Nov. 2, 1938, having developed severe abdominal pain without vomiting. Physical examination revealed a respiratory infection and acute laryngitis, and subsequently a tonsillectomy and adenoidectomy were done. Again the urinary findings were unchanged, and a urine culture revealed no growth. He was discharged and followed in the clinic. Within a month, for the first time, he began passing gravel in his urine. Occasionally he would pass rather large stones always associated with back and abdominal pain which at times was quite severe. When these stones were first obtained in December, 1938, they were assayed and found to contain 78 per cent calcium oxalate.

During the next two years he continued to have almost daily passage of gravel and, fairly frequently, large stones. Symptomatically he was unchanged and continued to have polydipsia and polyuria. Ammonium chloride was given during this time, and the acid condition of his urine was maintained. His blood pressure remained below 110/70. Repeated urine cultures showed no growth.

He was readmitted to the hospital for the fourth time on Oct. 7, 1940. During this period he had been unchanged symptomatically, although the ammonium chloride had been given only intermittently during the preceding six months' period. A flat film of his abdomen was unchanged. Repeated urinary cultures again showed no growth except that on one occasion *Streptococcus faecalis* was grown. He was treated with ammonium mandelate only until his urine was again sterile. Ammonium chloride was administered again in an effort to keep the urine acid and dilute, to prevent further precipitation of calcium salts, and in the hope of gradually dissolving the calcium carbonate and the calcium phosphate portions of the stones. An acid ash diet was also begun because there had been some vomiting of the ammonium chloride and it was thought necessary to rely on the diet to obtain an acid urine. All oxalate-containing foods were prohibited; calcium intake was restricted somewhat, and he was given rather large amounts of vitamin A without extra vitamin D. He was again discharged to be followed in the outpatient department. He continued to pass gravel and stones. On several occasions films of the abdomen revealed the same findings. He was hospitalized on various occasions because of acute renal colic and, with subsidence, would be discharged.

His seventh hospital admission was on Jan. 4, 1942, three and one-half years after his initial hospitalization. Because of chills, fever, abdominal pain, and vomiting, the diagnosis was ureteral colic. For the first time an elevated non-protein nitrogen of 49.0 mg. per cent was found. Ammonium chloride had been practically discontinued at that time because of the vomiting that occurred when it was given, and he was maintained primarily on the acid ash diet and restriction of calcium and oxalate in his foods. Because there had been no essential change and certainly no x-ray evidence of dissolution of the stones, in Novem-

ber, 1942, sodium citrate was begun in doses of approximately 10 Gm. a day. For a while he improved symptomatically and passed fewer stones and less gravel, but later sodium citrate became ineffectual.

His eleventh hospital admission was on June 16, 1943. Symptomatically, he had remained unchanged. An Addis-Shevky concentration test revealed that the maximum concentration at that time over a twenty-four hour period was 1.012. During this period of hospitalization cystoscopy and retrograde pyelography were done. A few crystals came from the right ureter, a few pus cells from the left ureter, but no bacteria. On cystoscopy the bladder was found to be normal, and on retrograde pyelography the dye was seen in the pelves, major and minor calices, and both ureters. The pelves appeared to be of normal size; the calices were somewhat blunted because of the large calculi which they contained. After much consideration and consultation with the Genito-Urinary Department it was agreed that operative removal of the stones would be impossible inasmuch as the multiple calculi which were scattered throughout the pelves were intrarenal. This would have necessitated multiple incisions through renal substance to evacuate the stones and would have been mechanically impossible. As demonstrated by the Addis-Shevky concentration test and the elevated nonprotein nitrogen, there was definite evidence of more severe renal damage; and it was doubtful if further therapy would change the picture. However, sodium citrate was continued for about one year without change in the x-ray findings. He was again followed in the outpatient department, and hospitalization was necessary because of renal colic. He continued to pass gravel and stones. Repeatedly in the outpatient department his blood pressure and blood chemical findings remained normal except that the nonprotein nitrogen gradually increased. (Table I.)

On May 24, 1947, he was readmitted to the hospital for the fourteenth time, experiencing severe ureteral colic, and on x-ray of the abdomen a stone was found in the right ureter at the ureterovesicle junction. (Fig. 1.) Attempts at catheterization of the right ureter were unsuccessful, so that on June 7, 1947, a right ureterolithotomy was done with removal of a small stone at the ureterovesicle junction. Recovery from this was prompt and uncomplicated. Roentgenograms of the chest and skull remained negative. The serum nonprotein nitrogen was 92 mg. per cent prior to operation, 160 mg. per cent at the time of operation, dropping to 96 mg. per cent postoperatively.

During this admission balanced urinary calcium studies were done using a weighed diet of 0.994 Gm. calcium (20 mg. per kilogram) as advised by Knapp.[13] He vomited some of it, but on June 3, his urinary output was 3,130 c.c. containing the equivalent of 3 milligrams excretion of calcium for twenty-four hours. The test was repeated the next day with the same result. This excretion was almost negligible as compared to the normal values of Knapp.[13] It was therefore felt from the previous knowledge of the child and from the urinary calcium studies in particular, that there was no evidence of primary hyperparathyroidism.

In July, 1947, almost nine years after his first admission to the hospital, he developed severe symptoms and his condition became progressively worse. He had repeated episodes of pain and jerking of the legs which sometimes lasted several hours. There was rather marked stiffness of his legs early in the morning, and his muscles were quite painful. This would regress after he had arisen and exercised. His reflexes were generally hyperactive. At this time, his severe renal insufficiency was characterized by an elevated nonprotein nitrogen, phosphate retention, and bicarbonate reduction. At this time, however, the passage of gravel and stones decreased remarkably. To combat his tendency to acidosis, he received 1 c.c. per kilogram of molar sodium *r*-lactate and ample fluids to provide polyuria. His gait became somewhat jerky and wobbly, and on Aug. 25, 1947, he was readmitted to the hospital for the fifteenth and last time because of the occurrence of a severe generalized convulsion with typical carpopedal spasm and other signs of tetany. He had marked anemia with a hemoglobin count of 5.1 Gm. per cent. Multiple trans-

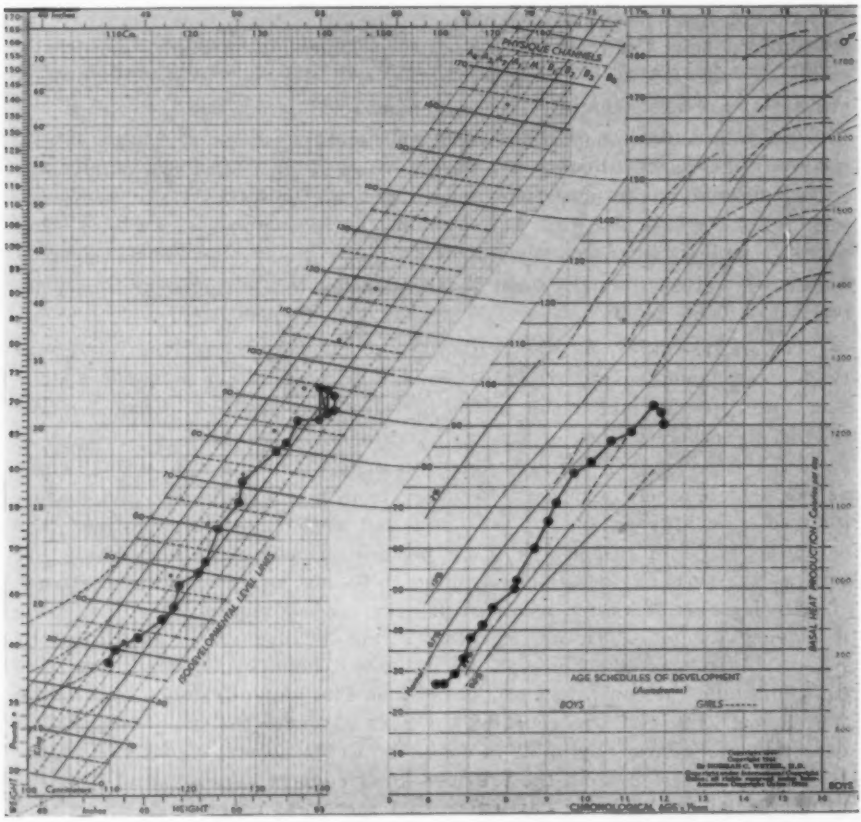

Fig. 2.—Growth and development as pictured on the Wetzel Grid.

fusions were given. His convulsions and tetany were at first controlled by the intravenous administration of calcium gluconate in doses of 0.25 c.c. per kilogram in a 10 per cent solution, but subsequent to each administration of calcium he developed rather severe hypertension; therefore magnesium sulfate in 25 per cent solution 0.1 Gm. per kilogram intramuscularly, was given to control the convulsions. His renal insufficiency progressed with further elevation of the nonprotein nitrogen, acidosis, phosphate retention, polyuria, and a urinary specific gravity of 1.001. (Table I.) He experienced two episodes of severe renal colic with the passage of large stones. He was also given one-sixth molar sodium *r*-lactate intravenously to help combat the acidosis and to provide fluid intake. On Sept. 17, 1947, twenty-three days after admission, he developed a generalized precordial friction rub, became comatose, and despite all subsequent efforts, expired on Sept. 19, 1947.

It is interesting to note in the nine years we observed this boy, that despite the severity of his renal insufficiency over such a long period, his growth and development as evaluated on the Wetzel Grid (Fig. 2) was excellent until terminally.

Necropsy.—Examination was performed three and one-half hours after death. External examination of the well-developed and well-nourished body revealed no abnormalities other than petechiae and ecchymoses in the skin and a 12 centimeter scar of a surgical incision in the right lower quadrant of the abdomen. The appendix was absent, and there were a few petechiae in the mucosa of the bladder and small intestine. More significant observations were as follows:

There were 200 c.c. of clear straw-colored fluid in the peritoneal cavity and 125 c.c. of a similar fluid in each of the pleural cavities. In the precordial cavity were 50 c.c. of a clear yellow fluid and both surfaces of the pericardium were covered by a slight amount of friable fibrinous material. The heart weighed 265 grams compared to the average normal weight for this age of 124 grams. The urinary bladder was distended to the level of the umbilicus with a reddish-colored urine.

Four tan-colored parathyroid glands had a total weight of 188 milligrams. Petechiae were visible within the substance of two of them. The kidneys were stony hard to palpation, with a remarkable gritting sensation. The capsules stripped without difficulty, revealing grayish granular surfaces with minute white nodules and in which there were a few petechiae. The kidneys could not be cut in the ordinary fashion, but had to be dissected. The pelves contained many small hard irregularly-shaped stones, and large dumbbell-shaped stones of a similar material were impacted in the calices (Fig. 3). All of the stones were a light brown color on their outer surfaces and white on the inside. Some of them tended to fragment easily, but they were not chalky or soft. The thickness of the remaining kidney substance averaged only 6 millimeters (Fig. 4). It was firm and fibrotic and felt as though small particles of hard solid material were imbedded within it. The pelves and ureters were only very slightly thickened.

Microscopically, the kidneys presented a striking picture. The normal renal architecture had been completely disrupted. (Fig. 5.) The few recognizable glomeruli were separated and disarranged by intervening fibrous tissue. The glomerular tufts appeared to be slightly increased in cellularity, and there was thickening of the Bowman's capsule. The tubules were frequently dilated, and some of them contained granular debris or desquamated tubular epithelial cells. There were several large foci of lymphocytic infiltration and a relative increase in the number of small blood vessels. The walls of the vessels were not

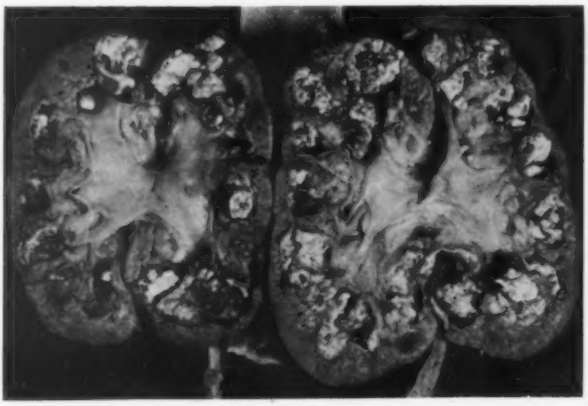

Fig. 3.—Kidney substance greatly reduced by the large irregular stones.

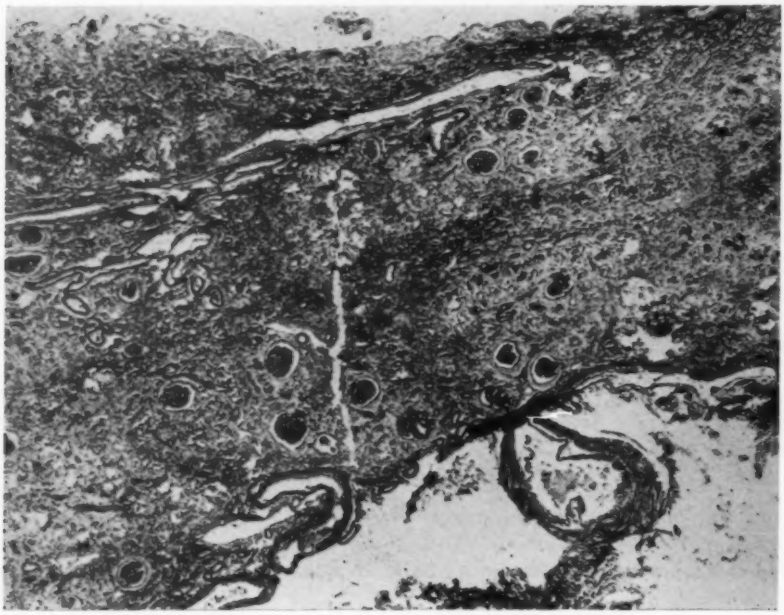

Fig. 4.—Total thickness of renal parenchyma averaged only 6 mm.

thickened or necrotic. A few small bluish-staining foci resembling calcium deposits were seen, but much more striking were the large number of focal areas containing doubly-refractile crystalline material. These crystals were of inconstant shape, sometimes elongated, radially arranged, usually unstained or rarely faintly basophilic. They were seen throughout the renal substance including the tissues adjacent to the pelvis. Through a polarizing microscope, they refracted light of different wave lengths to give a varigated appearance with many colors.

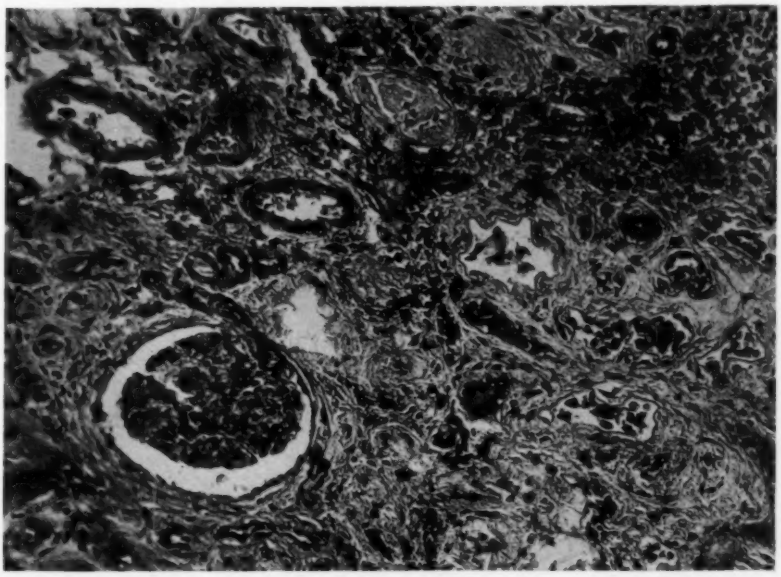

Fig. 5.—Note increased fibrous tissue, tubular atrophy, inflammatory cells, and foci of radially arranged crystalline material in the kidney. Hematoxylin and eosin stain.

There were no gross abnormalities of the bone, and the microscopic appearance of the costochondral junction was normal, as were hematopoietic elements. However, within some of the marrow spaces and in a few of the bony trabeculae there were foci of crystalline material identical in appearance but less frequent in amount than in the kidneys. (Fig. 6.) Sections of the rib, femur, and vertebrae showed these changes.

Four parathyroid glands were uniformly cellular with little or no fat infiltration. Numerous vascular channels were engorged with red blood cells, and there were small foci of hemorrhage in two of the glands. The majority of the cells composing the glands were large, had regular round or oval, somewhat vesicular, fairly basophilic nuclei, and clear cytoplasm. At times the cells were arranged in the form of a pseudoacinus with a scant amount of central homogeneous eosinophilic material. Several foci of six to eight even larger cells of the water-clear type were seen. No oxyphil cells were noted.

Post-mortem blood cultures, aerobic and anaerobic, yielded no growth during a period of thirty days' incubation.

The final anatomic diagnosis included: advanced nephrolithiasis with deposits of crystalline material compatible with calcium oxalate in the renal parenchyma, and in the rib, vertebrae, and femur; fibrous scars in the renal cortices; enlargement of the parathyroids; hypertrophy and dilatation of the heart; chronic passive congestion of the spleen; serofibrinous pericarditis; slight bronchopneumonia; bilateral hydrothorax; focal atelectasis of the lungs; ascites; fatty metamorphosis of the liver; petechiae and ecchymoses in skin, mucosa of small intestine, gums, bladder, renal cortices, parathyroid glands, and the capsule of the spleen; ulceration of the buccal mucosa; caseocalcified nodule in the upper lobe of the left lung; calcified nodule in left tracheobronchial lymph node; calcified nodules in the spleen; and healed surgical scar in the right lower quadrant of the abdomen and absence of the appendix (history of ureterolithotomy).

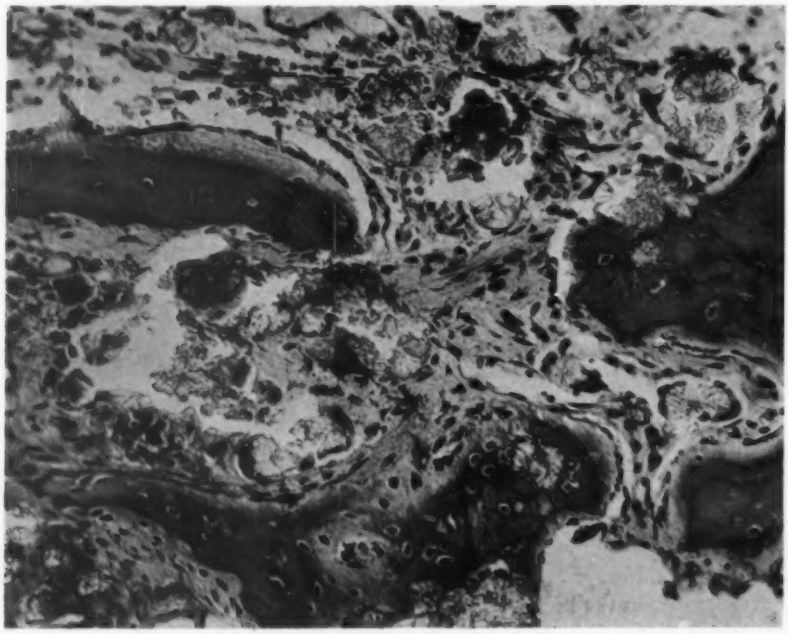

Fig. 6.—The crystalline material was in foci in the trabeculae as well as in the marrow of of the bones examined. Hematoxylin and eosin stain.

Chemical studies were performed to determine the nature of the crystalline material. Analysis of the stones in the renal pelvis showed 38 per cent ash of which 68 per cent was calcium, or 26 per cent of original stone was calcium. The stones contained 49 per cent oxalate by titration, traces of uric acid and phosphates, negligible carbonates, and no sulfates. On the basis of the independent calcium and oxalate determinations the stones were either 71 or 83 per cent calcium oxalate.

The crystals within the tissues had the same solubilities in alcohols, acids, and alkalies as the renal calculi or pure preparations of calcium oxalate. Stains for phosphates by the von Kossa method were negative, as were alizarin red S stains for ionizable calcium. It was felt that the relatively insoluble calcium oxalate did not ionize sufficiently to stain with alizarin red S. Some of the renal calculi probably arose by ulceration of crystalline masses from the renal papillae into the renal pelvis. Although the histochemical studies did not provide absolute identification of calcium oxalate within the tissues, they did indicate that there was a great probability that it was the chief component of the crystals.

DISCUSSION

The etiology of renal lithiasis is as varied as is the composition of urinary calculi, which may consist of pure or mixed forms of uric acid, urates, cystine, and calcium oxalate in acid urines and calcium oxalate, carbonate, and phosphate and ammonium magnesium phosphate in alkaline urines.[8, 10]

Sendroy[11] summarizes what is known of the production of stones. There is one chemical mechanism common to all: namely, the formation of crystals of one or more substances insoluble in the urine of a particular composition. Various factors may be responsible for the chemical reactions leading to the precipitation of crystals which occurs even in normal urine. However, such crystallization normally results in the production of sediment, not stones. Two essential factors, namely, urine composition and the availability of an organic matrix, represent the dual nature, chemical and pathologic, of the pathogenesis of calculus formation.

As causative factors in the disturbed mineral metabolism leading to renal calculus formation, the following have been cited on the basis of clinical and experimental evidence: (a) abnormal diet or medication (vitamin A deficiency, deficiency of calcium or magnesium, excess of calcium or phosphorus, excess of alkaline foods, or, less frequently, of acid foods); (b) chemotherapy (sulfa drugs, salicylates); (c) stasis or urethral pressure (age, pregnancy); and (d) urinary infection (usually associated with urea-splitting bacteria).[11]

Faconi[12] described three cases of infants with cystine crystals in various organs including the kidneys, bone marrow, spleen, liver, lymph nodes, salivary gland, thyroid, parathyroids, and adrenals, and reviewed the literature on this disease. The patients showed dwarfism, rickets or pseudorickets, nephrosclerosis without hypertension, anorexia, obstipation, polyuria, permanent albuminuria, intermittent glycosuria, thermolability and hypoplasia of the thymus. These individuals with a cystine metabolic defect differed clinically as well as in the physical and chemical properties of the crystals from the case reported here.

Apparently, none of the usual factors existed in this patient. The absence of repeated or chronic urinary infection and other possible etiological factors, the long period of fairly adequate compensation and normal development, and below-normal levels of calcium excreted in the urine are all clinical indications of the unusual character of this case. The case differs from the usual renal rickets in that the parathyroids were not greatly enlarged, fibrosis of bone

marrow spaces was absent, and most important, calcium oxalate crystals were present in the bone and kidneys. The presence of crystalline deposits in bone and bone marrow is rare. Although urate crystals are found in bones in gout, on the basis of solubility and other properties, these crystals were not urates. The autopsy findings of the doubly refractile crystals, presumably calcium oxalate in the kidneys and bone add to the suggestion that there was some defect in the calcium or oxalate metabolism of this patient.

SUMMARY

A case of nephrocalcinosis of unknown etiology in a boy is reported with calcium oxalate crystals in the kidneys and bones. The patient was followed for nine years with death at the age of 12 years. Few, if any, comparable cases are reported in the literature and it is suggested that this patient had an unusual disturbance of calcium oxalate metabolism.

Throughout his long course of study and treatment this patient remained under the immediate supervision of Dr. A. F. Hartmann, to whom we are indebted for encouragement in submitting this report.

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PLASMA "ALKALINE" PHOSPHATASE ACTIVITY

I. Normative Data for Growing Children

Leland C. Clark, Jr., Ph.D., and Elizabeth Beck, M.S.
Yellow Springs, Ohio

AS PART of a study of the relationship of various blood enzymes to the growth and development of children, a study of plasma alkaline phosphatase has been undertaken. It is hoped that the study will serve the purpose of supplying normative data and that description of the nature of the changes in level of this enzyme in the plasma will help to elucidate the regulating factors.

METHOD

The analyses reported have been conducted on blood samples obtained from the children enrolled in the research plan of the Institute and from college students. The blood samples were collected between January and March at yearly intervals for four years. In all cases blood was collected by finger puncture, centrifuged in Pyrex capillary tubes, and the plasma was analyzed in duplicate by the procedure of Bessey[1] under carefully controlled conditions. A Model DU Beckman spectrophotometer was used for the measurement of the p-nitrophenol liberated from p-nitrophenyl phosphate by the enzyme.

The standard error of duplicate determinations on a random sample of seventy-five analyses was ±1.14 per cent, indicating a high precision for the procedure.

DATA

The data obtained are tabulated according to age and sex groups (Table I) in such a way as to facilitate the use of the norms for clinical work. An inspection of the data reveals a very wide range of values in each age group while examination of Fig. 1 reveals certain well-defined trends in the plasma alkaline phosphatase activity with regard to age. There is a marked drop during the first year of life, followed by a plateau until about the age of 10 years when the mean value for the girls drops precipitously and the value for boys rises until the age of 13 years and then drops. The mean sex difference which appears at this time continues at least until the age of 27 years. Samples obtained from college students were used to obtain the data for the 19- to 27-year age group.

The year-to-year correlations obtained (Table II) indicate that a given child tends to stay at a particular level from year to year. One may conclude that a single sampling every year would, generally speaking, be sufficient to classify a child regarding plasma alkaline phosphatase activity.

Bodansky[2] and Gould[3] have shown, using β-glycerophosphate as a substrate, that the alkaline phosphatase activity of extracts of bone and kidney are strongly

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From the Fels Research Institute for the Study of Human Development, Antioch College, Yellow Springs.

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TABLE I. PLASMA ALKALINE PHOSPHATASE FROM BIRTH TO TWENTY-SEVEN YEARS OF AGE

AGE GROUP (YR.)	AVERAGE AGE (YR.)	SEX	NO.	RANGE	MEAN	SIGMA
0.0- 1.0	0.5	M	43	5.17-12.60	8.48	1.79
		F	17	5.13-11.10	7.55	1.71
		T	60	5.13-12.60	8.22	1.82
1.1- 2.0	1.7	M	11	4.46- 8.76	6.75	1.13
		F	12	3.82-10.40	6.59	1.87
		T	23	3.82-10.40	6.67	1.56
2.1- 4.0	3.2	M	10	3.82- 7.66	5.87	1.22
		F	9	4.56- 7.64	6.31	1.00
		T	19	3.82- 7.66	6.08	1.14
4.1- 6.0	5.0	M	20	4.12- 7.65	6.26	1.02
		F	10	5.50- 9.45	6.90	1.21
		T	30	4.12- 9.45	6.47	1.13
6.1- 8.0	7.1	M	44	4.14- 8.06	5.93	1.05
		F	33	2.81- 9.63	6.21	1.46
		T	77	2.81- 9.63	6.05	1.25
8.1-10.0	8.9	M	34	4.34-11.48	6.51	1.64
		F	31	4.56- 9.44	6.71	1.51
		T	65	4.34-11.48	6.62	1.58
10.1-12.0	11.0	M	22	1.81-11.10	5.85	2.03
		F	38	3.13- 9.68	5.98	1.59
		T	60	1.81-11.10	5.93	1.77
12.1-14.0	13.0	M	30	3.79-14.00	7.26	2.25
		F	43	1.78- 8.44	4.79	1.71
		T	73	1.78-14.00	5.81	2.30
14.1-16.0	15.0	M	28	3.26- 9.35	6.14	1.92
		F	35	1.74- 7.98	3.38	1.57
		T	63	1.74- 9.35	4.61	2.21
16.1-18.0	16.9	M	27	1.65- 5.12	3.02	0.953
		F	23	1.44- 3.15	2.19	0.477
		T	50	1.44- 5.12	2.64	0.876
18.1-20.0	18.1	M	9	1.31- 4.00	2.82	0.846
		F	4	1.38- 2.04	1.77	0.273
		T	13	1.31- 4.00	2.50	0.786
18.1-20.0	19.0	M	6	2.08- 3.94	2.99	0.687
		F	26	1.60- 4.49	2.26	0.615
		T	32	1.60- 4.49	2.40	0.680
20.1-22.0	21.0	M	10	2.12- 4.38	3.02	0.693
		F	11	1.39- 3.13	2.24	0.583
		T	21	1.39- 4.38	2.61	0.752
22.1-24.0	23.0	M	14	1.58- 4.36	2.50	0.634
		F	6	1.35- 2.58	2.05	0.424
		T	20	1.35- 4.36	2.36	0.634
24.1-26.0	25.0	M	11	1.29- 3.46	2.24	0.594
26.1-28.0	27.0	M	6	1.51- 4.29	2.47	0.906
Total			1.252	1.29-14.00		

TABLE II. RELATIVE CONSTANCY OF PLASMA ALKALINE PHOSPHATASE FROM YEAR TO YEAR

	CORRELATION COEFFICIENTS
YEAR	r*
1946-1947	0.573
1947-1948	0.818
1948-1949	0.672

*r is the product-moment correlation[29] obtained when the uncorrected raw data are used. If corrections for normal age changes were made they would tend to increase the correlation.

inhibited by taurocholate while those from intestine are not. We have confirmed these findings using p-nitrophenyl phosphate as a substrate. Furthermore, it was found that the alkaline phosphatase activity of placental extracts is not inhibited by taurocholate. Table III summarizes these data and reveals, in addition, the fact that the phosphatase activity of plasma obtained from growing children is inhibited about 50 per cent by taurocholate. These data conform with the assumption that the plasma alkaline phosphatase activity of growing children is derived largely from osteoid tissue. This assumption gains additional support when the normative data for plasma alkaline phosphatase are compared (Fig. 2) with normative data[4] for *rate* of growth of bones as indicated by height measurements.

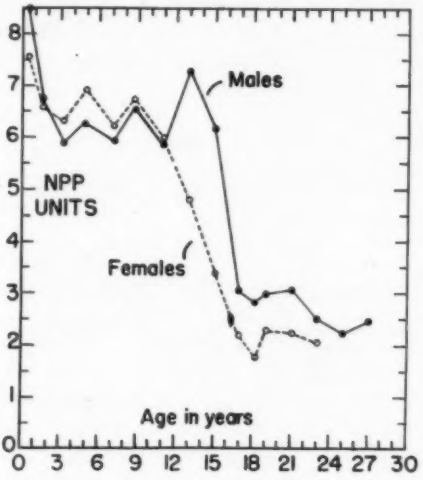

Fig. 1.

Fig. 3 compares the normative data obtained by Bessey,[5] Harrison,[6] and ourselves. It can be seen that there is general agreement concerning the sex difference at pubescence, the rapid fall during pubescence, and the fact that male children reach a peak plasma alkaline phosphatase activity at the age of 13 years. Our data do not indicate a rise in enzyme activity in girls as do the

TABLE III. TAUROCHOLATE INHIBITION

TISSUE SOURCE	RELATIVE ACTIVITY OF ALKALINE PHOSPHATASE IN THE PRESENCE OF TAUROCHOLATE*		
	BODANSKY (%)	GOULD (%)	OURS (%)
Kidney	47- 58	29.3	49-54
Bone	47- 56	30.1	43-56
Intestine	96-100	78.9	100
Placenta	—	—	100
Plasma† M	—	—	49.6 ± 7.0
F	—	—	51.7 ± 10.1

*The taurocholate concentration was 0.00625 M as used by Bodansky.[3]

†The data for plasma alkaline phosphatase were obtained from thirty-two boys and twenty-nine girls between the ages of one and 18 years. The numbers given represent the mean and standard deviation.

data of Harrison. The differences in the absolute average values are very likely due to differences in the groups tested, although slight differences in technique may also contribute to a minor degree. The normative data of Mulay,[7] Vermehren,[8] and Pimenta[20] show the same general trends with age. The reports of Klasmer[9] and Barnes and Munks[10] apply only to infancy.

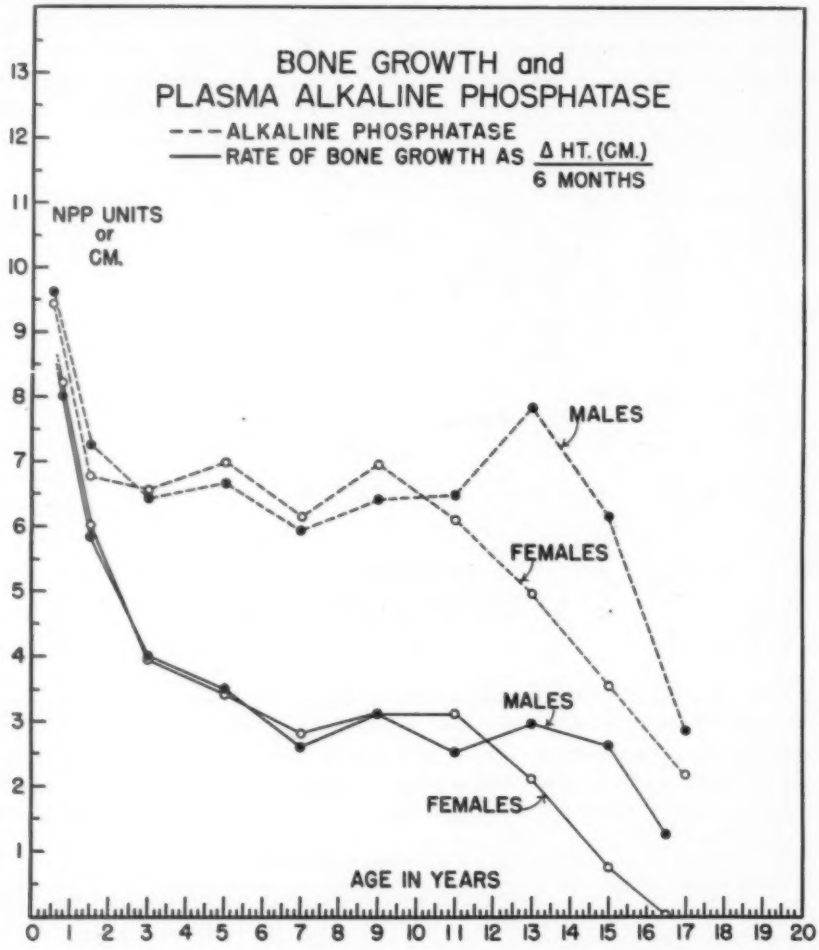
BONE GROWTH and
PLASMA ALKALINE PHOSPHATASE
---ALKALINE PHOSPHATASE
——RATE OF BONE GROWTH AS Δ HT. (CM.) / 6 MONTHS
NPP UNITS or CM.
MALES
FEMALES
MALES
FEMALES
AGE IN YEARS
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
1 2 3 4 5 6 7 8 9 10 11 12 13

Fig. 2.

Fig. 4 indicates the relationship between 17-ketosteroid excretion and the level of plasma phosphatase activity in six normal, healthy children. It would appear from these data that as the ketosteroid excretion increases, the plasma alkaline phosphatase activity decreases. However, a limited number of observations of a case of adrenogenital syndrome with 17-ketosteroid excretion exceeding

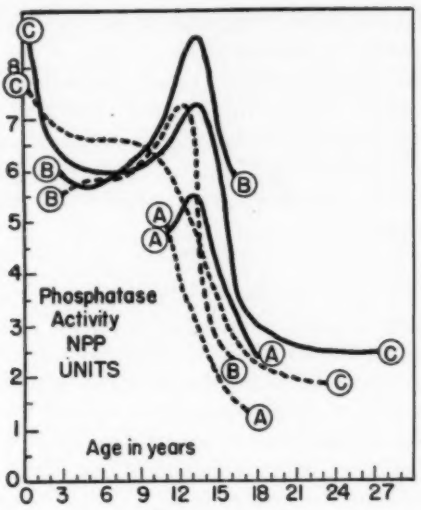
Phosphatase
Activity
NPP
UNITS
Age in years
0 3 6 9 12 15 18 21 24 27

Fig. 3.

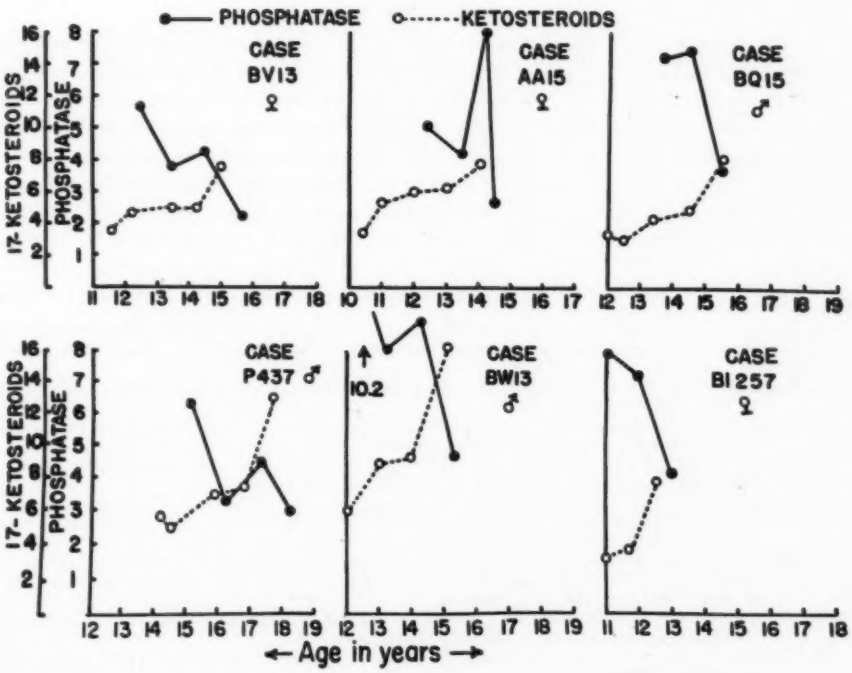
PHOSPHATASE
KETOSTEROIDS
17- KETOSTEROIDS
PHOSPHATASE
CASE BV13 ♀
CASE AA15 ♀
CASE BQ15 ♂
CASE P437 ♂
CASE BW13 ♂
10.2
CASE BI 257 ♀
← Age in years →

Fig. 4.

adult values indicates that high phosphatase levels were maintained. Thus, the apparent relationship may not be causative.

Following the suggestion of Bessey,[5] there has been a tendency to interpret values exceeding 8 units as indicative of poor nutrition. However, Harrison[6] could find no evidence of pathology in the group of children with values exceeding 8 units which she studied. Clinical and roentgenologic examination of the school-age children in our group who had values over 8 units likewise revealed no evidence of pathology.

DISCUSSION

The data indicate a general parallel between growth rate as measured by height and the plasma alkaline phosphatase activity. Although no data have as yet been reported for the level of growth hormone in the blood and urine of children, the finding reported by Li and associates[11] that growth hormone causes a significant increase in the plasma phosphatase activity in rate may be regarded as evidence that plasma phosphatase activity in children reflects the growth-promoting activity of the anterior pituitary. That other factors may operate in pathologic conditions associated with the thyroid,[12, 13] parathyroid,[14, 15] and certain nutritional deficiencies,[9, 10, 16-18] is clear.

SUMMARY

Plasma alkaline phosphatase is high in infancy, then drops by the second year of life to a plateau which lasts until pubescence. At 9 years of age in girls and 11 years of age in boys a rapid drop occurs, until by the seventeenth year of life adult values are found. The sex difference which begins at pubescence diminishes gradually until the age of 20 but persists into adulthood, in male subjects higher than in female. The plasma alkaline phosphatase activity seems to be closely related to growth rate as indicated by height measurements and to be derived largely from osteoid tissue as indicated by taurocholate inhibition studies.

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INTELLIGENCE QUOTIENT OF CHILDREN WHO HAVE RECOVERED FROM ERYTHROBLASTOSIS FETALIS

JOAN M. GERVER, M.A., AND RICHARD DAY, M.D.
NEW YORK, N. Y.

KERNICTERUS develops in about 15 per cent of babies who suffer from erythroblastosis fetalis.[1] Those who die with this complication have yellow pigmentation of the basal ganglia, the hippocampal gyrus, and other areas of the gray matter of the brain and spinal cord. Microscopic examination sometimes discloses degeneration of nerve cells in the pigmented areas. Those infants who survive manifest varying degrees of muscular paralysis, spasticity, and motor incoordination. Until recently it has been generally believed that injury to nervous tissue leading to these motor signs is an all-or-none phenomenon. According to this view those babies who escape without evidence of motor disability recover from the anemia without residual difficulties and develop as entirely normal individuals. Yannet,[2] however, has asserted that in a group of mentally deficient children there were significantly more children than expected who were Rh positive and had Rh-negative mothers. His interpretations have been questioned.[3] In order to determine the extent of mental impairment resulting from erythroblastosis fetalis, we have administered the Stanford-Binet intelligence test to a group of children whose record of neonatal illness was available to us. We felt that such a survey would lead to a better assessment of the hazards of this form of hemolytic disease. The findings should also show whether the injury to nervous tissue, like the other manifestations of the disease, occurs with wide variations in severity.

METHODS

The Stanford-Binet test was selected because the results are expressed by a number which has the same significance for children of different ages, a feature which facilitates statistical comparison. It can be used only in children whose mental age is at least 2 years. Our primary interest has been in the superficially normal children and not in those with impairment of motor capacity. One of us (J. M. G.) administered all of the tests.

CASE MATERIAL

The children of the study were drawn from four hospitals, so that there has been lack of uniformity in diagnostic procedures and treatment. The minimum diagnostic criteria demanded were as follows: (1) The clinical diagnosis of erythroblastosis fetalis, icterus gravis, or anemia of the newborn infant had been made in the neonatal period. (2) Jaundice had been apparent to the eye. (3)

From the Department of Pediatrics, College of Physicians and Surgeons, Columbia University, and the Babies Hospital, New York. Additional cases for this study were obtained through the kindness of The New York Hospital, The Hartford Hospital, and Mt. Sinai Hospital, New York, and from Dr. Peter Vogel, New York, and Dr. Philip Levine, Somerville, N. J.

Aided by grants from the John and Mary R. Markle Foundation, from the Coordinating Council for Cerebral Palsy in New York City, and from the Rockefeller Foundation.

Anemia sufficient to lead to at least one transfusion had occurred. (4) Either laboratory evidence, or the subsequent course of the illness, or both had yielded strong evidence against a diagnosis of syphilis, sepsis, biliary obstruction, toxoplasmosis, hepatitis, physiologic jaundice, or familial hemolytic anemia. (5) There was a living first-born child who had not had any neonatal jaundice or anemia. (6) The child must possess an Rh factor absent in the mother. (7) If tests for Rh antibodies had been performed on the mother near the time of delivery (as was the case for the forty-five younger children in the group), those tests must have been unequivocally positive.

Since we are not reporting on the intelligence of every child whose neonatal record came to our attention, possible causes of bias in the selection of cases must be considered, as follows:

1. There were a certain number of known and no doubt many unknown mild cases of the disease which were either missed or excluded because of failure to meet the criteria given above. With the sensitive serological techniques now available, permitting more reliable criteria for the diagnosis of erythroblastosis, an investigation undertaken at the present time could legitimately include such cases. Our group does represent a selection of cases, so far as severity is concerned, which would differ from a selection based on other criteria. This aspect of the selection of cases will become important when evidence as to the effect of replacement transfusion on mentality becomes available. Since the Stanford-Binet test is more easily applied to older children, and in them yields probably more accurate measurements of intelligence, we have retained in our series those children whose illness dates from an era prior to accurate Rh testing. Actually, these older subjects do not have a lower I. Q. than the younger.

2. Children brought to us because of a suspected defect have been excluded. Only those children have been included who were sought out by us as a result of our inspection of the neonatal record.

3. A good many children whose records fulfilled the requirements were not seen. In most instances, failure to make contact with the patient arose from the family having moved without leaving a forwarding address. There is nothing to indicate that the severity of the erythroblastosis was different among the lost families. Only one family refused to cooperate, so it can be confidently asserted that our series is not biased as a result of parental judgment as to which cases were made available.

4. Many of our children were private patients and all of them were cared for in hospitals charging a substantial fee. These two factors may have tended to raise the intelligence score of the group.

RESULTS

Intelligence.—For the reasons given above, the children we studied might be expected, in the absence of any effect of illness, to have an I. Q. above that of the population as a whole. In order to determine if they did have any mental impairment, it would not suffice to compare their scores with the population mean of 100. To meet this difficulty we have used for our analysis only those scores made by children who had an older brother or sister with a record free of

any neonatal illness. The older siblings served as a control group with the closest possible hereditary and environmental background. There were sixty-eight such pairs of children whom we tested, the younger child in each pair having had erythroblastosis fetalis and the older having escaped. None of these children had any motor nerve difficulties, and none had been diagnosed as having had kernicterus. The group with such signs is discussed separately.

The average I. Q. of the affected children was 102.7, and their average age was 4.5 years. The average I. Q. of the sixty-eight members of the control group of older siblings was 114.5 and their average age was 9.8 years. The affected group ranged in I. Q. from 69 to 133, with a standard deviation of 14.1. The control children ranged in I. Q. from 78 to 156 with a standard deviation of 16.4.

The mean difference in I. Q. of 11.8 would be of relatively little importance in considering the case of a single child. Statistical analysis reveals, however, that the chance for the occurrence of such a difference, were there really no inferiority of the affected siblings, is only one in a million.*

Not all of the affected children had I. Q.'s lower than the family control. Table I indicates the frequency with which the affected and the unaffected children fell into each of three I. Q. categories. There is a highly significant excess of affected children in the low category and a similar excess of unaffected children at the upper end of the intelligence scale. Chi square calculated from this table is 14.7, which means that the probability is 1 in 1,000 that the observed difference in distribution should arise from chance. It can be concluded from this table that the explanation of the lower mean value for the intelligence of the affected children does not lie in the presence of a small group of children with very low intelligence.

TABLE I*

I. Q.	AFFECTED CHILDREN	CONTROL CHILDREN	TOTAL
111 or higher	19	40	59
91-110	36	24	60
90 or lower	13	4	17
Total	68	68	136

*Chi square calculated from this table is 14.7, which indicates that it is highly improbable that a distribution as biased as this would arise by chance from a common population.

Further support of the idea that the fraction of the affected children who suffered some mental impairment is large is obtained from inspection of the frequency distributions portrayed in Fig. 1. In the construction of the figure the Stanford-Binet scores obtained by the children who lacked an available older sibling have been added to those of the sixty-eight children considered above as well as four additional control cases. Were there a small number of seriously damaged children, the others being undamaged, a bimodal type of distribution would have resulted. Actually, the distribution for the affected children is unimodal and is slightly displaced to the low side of the mean for the unaffected control children.

*The data were analyzed in pairs. The mean difference, 11.83, was tested against zero by student's "t" test.[4] The standard error of the mean difference was found to be 1.99.

It can be concluded that there is some factor which has caused a variable, widespread, and usually moderate lowering of the intelligence of the affected children as tested by the Stanford-Binet score.

Is it possible that the cause of the inferiority lies not in the erythroblastosis but in the younger age of the affected children? Did the psychologist tend to assign a lower score to the young children? We have looked into such a possibility in two ways; by analyzing twenty-eight pairs of children from families entirely free of erythroblastosis fetalis and by calculating the correlation between age and I. Q.

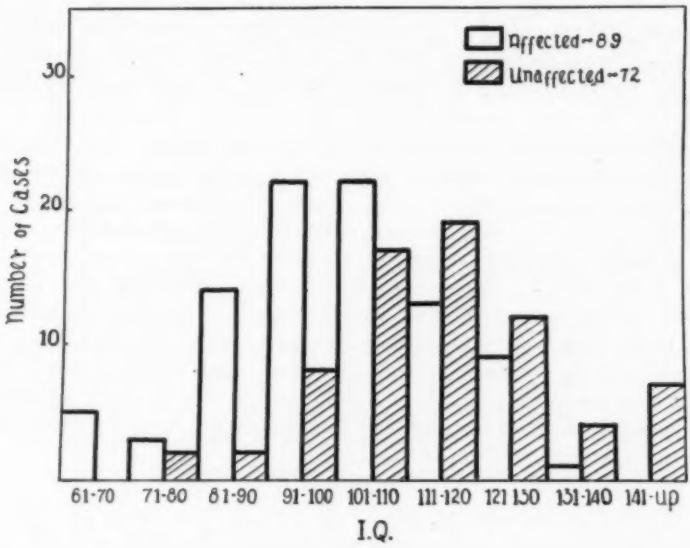

Fig. 1.

The twenty-eight control families were drawn from the records of Sloane Hospital for Women. There were no private patients among these families, a factor which might lower the mean score of the group. Families were selected by number from among those in which there were at least two children born at Sloane Hospital who had not had any serious illness and whose neonatal course was uneventful. The intelligence scores obtained by these children appear in Table II, together with a summary of those obtained by the sixty-eight pairs of children from the affected families. The slight superiority of the younger children in the control families is not of statistical significance. The age spread is very similar to that in the affected families.

The coefficient of correlation of age with I. Q. among the sixty-eight affected children is –0.086. In the case of the unaffected siblings the figure obtained was –.046, a value likewise not significantly different from zero. In this sample there is certainly no evidence of the dependence of I. Q. on age.

TABLE II*

	FAMILIES WITH ERYTHROBLASTOSIS		FAMILIES FREE OF ERYTHROBLASTOSIS	
	AFFECTED CHILDREN	UNAFFECTED CHILDREN	YOUNGER CHILDREN	OLDER CHILDREN
Number	68	68	28	28
Mean I. Q.	102.7	114.5	111.1	109.2
Mean age (yr.)	4.54	9.76	4.93	9.14

*The slight superiority of the younger children from the control families is not statistically significant.

One cannot say, from this analysis, that the influence of the erythroblastosis was specific. It is conceivable that any neonatal illness might have the same consequence or that any child ill in the neonatal period is treated differently by the parents. If such factors are operative to an extent sufficient to lower the average I. Q. by 11 points, a field of investigation of considerable interest is suggested.

Kernicterus.—We have examined a total of 100 children recovered from erythroblastosis (thirty-two of these were not included in the analysis given above for the reasons previously stated). There were eleven (11 per cent) who had motor difficulties. The more severely damaged children were typical of those described by many authors[5] as representing kernicterus. Several of the children were only mildly affected. None of those with motor difficulties were included in this group of sixty-eight children analyzed above. One child had been examined by one of us two years previously, at which time he was definitely spastic and had been slow in walking and talking. When seen later at 3 years of age his motor difficulties consisted solely of a slight tremor on find manipulations and slight strabismus. His speech, which had been poorly articulated, was normal.

RELATIONSHIP OF I. Q. TO OTHER FACTORS

Sex.—Table III indicates the mean I. Q.'s of the two sexes. No difference is evident. The differences in the control families are presumed to be the result of variation in a small series. The eleven children with motor difficulties included nine boys and two girls.

TABLE III

	FAMILIES WITH ERYTHROBLASTOSIS				FAMILIES FREE OF ERYTHROBLASTOSIS			
	AFFECTED CHILDREN		UNAFFECTED CHILDREN		YOUNGER CHILDREN		OLDER CHILDREN	
	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE	MALE	FEMALE
Number	39	29	36	32	11	17	18	10
Mean I. Q.	103.2	102	112.9	116.3	105.0	115.0	110.0	107.8

Birth Weight.—The coefficient of correlation of I. Q. with birth weight among the affected children is 0.065, a value which is not significantly different from zero. The average weight at birth of the children with motor involvement was 3,380 Gm., and of the others it was 3,301 Gm.

Severity of the Illness.—We found it difficult to assess the severity of the hemolytic process from the case records. There was a lack of uniformity in the frequency and timing of laboratory examinations and clinical notes. One item

which was faithfully recorded was the total amount of blood given during the course of the illness. Undoubtedly, more blood was given to infants with severe anemia than to those with slight anemia, although a great deal of variation in clinical judgment is to be expected concerning the indications for transfusion. Despite its many disadvantages, we feel that the best index of severity available from this set of records is the number and size of transfusions. Analysis reveals a correlation coefficient of 0.34 between I. Q. and the total amount of blood administered in individual cases. The probability is less than 0.01 that there is in reality no correlation. The value of 0.34 is low. However, considering the numerous known sources of random variation, the existence of any real relationship, however small in degree, cannot be disregarded. It is of interest, for example, that the association shown in these figures is not in line with the statement sometimes made that kernicterus is more likely to occur in those infants who have slight anemia than in those with severe anemia. The association is also of importance in excluding the possibility that unconscious bias on the part of the psychologist is responsible for the results reported in this paper. Although the psychologist necessarily knew whether she was testing an affected or an unaffected child, she did not know how much blood had been used in the treatment of the affected children.

The relationship of the degree of anemia to the I. Q. was also studied. The coefficient of correlation between the lowest recorded level of hemoglobin and the I. Q. was found to be 0.25, a figure lower than that found for the amount of blood transfused. Despite the small degree of association indicated by such a figure, it does reach the 5 per cent level of statistical significance and indicates a relation for the group as a whole. The conclusion previously drawn from the figures for the total blood administered is thus supported.

COMMENT

The purpose of this research has been to discover if there are children surviving erythroblastosis fetalis who suffer from mild impairment of mentality in addition to the well-recognized group who exhibit residual severe motor disability. Since the other clinical and laboratory manifestations of the disease show a great tendency to vary in severity, one would not expect a single feature, damage to nerve tissue, to be an exception. The definitely damaged children, those that we have diagnosed as truly suffering from kernicterus, are a rather varied group, some of whom are only mildly affected. A similar gradation is found in severity of damage among the children who appear normal but have been shown to have a moderate impairment in mentality: the depression in I. Q. score is not of much magnitude, on the average, and certainly is not sufficient to justify any alteration in the usually good prognosis given to parents of children who have escaped motor abnormalities. It is, however, a finding of biological significance in the study of the disease. One cannot say from the figures presented that the effect of the disease is specific. Perhaps any severely ill newborn infant will suffer some degree of permanent or perhaps long-lasting functional impairment of intellect. Perhaps a reexamination of the children will show improvement after a lapse of time.

SUMMARY

The average intelligence, as measured by the Stanford-Binet Scale, of a group of sixty-eight children recovered from erythroblastosis fetalis without suffering obvious motor nerve damage was found to be lower than that of their unaffected older brothers and sisters. Statistical analysis indicates that the inferiority is not likely to have resulted from chance nor from the circumstance that the affected child was always younger than his control sibling. The extent of the impairment is slight, the mean difference in I. Q. being only 11.8, so that there is no occasion for altering the usual custom of giving a good prognosis to the parents of a child who has apparently recovered from erythroblastosis without suffering motor nerve injury.

The data presented do not distinguish between a specific effect of the Rh antibody and a nonspecific one such as might be operating in any illness in the newborn period.

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NATAL AND NEONATAL TEETH

A Review of Twenty-Four Cases Reported in the Literature

Maury Massler, D.D.S., M.S.,* and Bhim Sen Savara, B.D.S., (Pb.); L.D.S., R.C.S. (Eng.); M.S.
Chicago, Ill.

INTRODUCTION

Definition of Terms.—"Natal teeth" have been defined as teeth which are present in the oral cavity of the infant at the time of birth, while "neonatal teeth" will in this paper refer to those teeth which erupt during the neonatal period (from birth to 30 days).

Prematurely erupted primary teeth present at birth have been described as "congenital teeth" or "fetal teeth" in early pediatric texts and dental literature. The term "dentitio praecox" has also been used and although this last is a more scientific term, it is also too broad to accurately define the teeth erupted at or near birth, since prematurely erupted permanent teeth may also be included. The various terms mentioned above have, in recent years, been discarded in favor of the term "natal teeth." For reasons which will become more apparent during the course of this review, the term "neonatal teeth" is also offered as a useful and descriptive term.

Definition of the Problem.—Natal and neonatal teeth constitute a problem for the attending obstetrician or pediatrician since the presence of such teeth may (a) be symptomatic of some underlying systemic disturbance and (b) may constitute a local problem during breast feeding or (c) may result in trauma to the infant's tongue. The question of the normality of the structures and whether such prematurely erupted teeth should be retained or extracted are questions which the obstetrician will refer to the pediatrician and which the pediatrician will often refer to the pedodontist.

Purpose of the Paper.—This paper is an attempt to review the recorded literature on the subject in order to establish the present status of our knowledge of this problem. An attempt was also made to discover any etiologic factors that may account for this anomaly from the analysis of those cases reported in the literature. The subject matter for this review was thus derived from (a) case reports of actual instances of natal and neonatal teeth and (b) a general review of the subject as presented in various textbooks.

It should be pointed out that there were actually few cases of natal teeth reported in the literature during the last fifty years. A search through the literature revealed only twenty-four cases reported. The data obtained from the twenty-four case reports are presented in Tables I and II. Unfortunately, only a few of these were accompanied by good histories or discussed the cause of the premature eruption of the teeth.

From the University of Illinois College of Dentistry, Chicago.
*Professor of Graduate Pedodontics.

TABLE I. ANALYSIS OF NATAL AND NEONATAL TEETH IN TWENTY-FOUR CASE REPORTS

CASE NO.	AUTHOR	YEAR	TYPE OF TEETH	TEETH AFFECTED	DESCRIPTION OF TEETH	AGE OF ERUPTION	SYSTEMIC CONDITION OF INFANT	CLINICAL SYMPTOMS	COMPLICATIONS	FAMILIAL TENDENCY	REMARKS
					A. Natal						
1.	Magitot	1883	?	Lower teeth	None		Healthy	None	Extracted Profuse hemorrhage	?	Died
2.	Ballantyne	1897	Primary	Upper centrals	Well formed		?	None	None	?	Present at 16 months
3.	Ballantyne	1897	Primary	Lower centrals	None		?	Teeth sloughed	Alveolar process necrosed	?	Infant died
4.	Ballantyne	1897	Primary	Lower centrals	Became soft		Congenital syphilis	Snuffles	Papular eruption	Syphilis from father	None
5.	Ballantyne	1897	Primary	Lower centrals	Soft and pultaceous		Bottle-fed	None	None	?	None
6.	Ballantyne	1897	Primary	Lower centrals	Normal		Breast-fed	None	None	?	None
7.	Krakovski	1902	Primary	One lower central	None		Feeble	Ulcerous gums	Ulcerated tongue	?	Upper centrals erupted at 2 months
8.	Rosenhaupt	1911	?	?	None		?	None	None	Present	None
9.	Schelling	1912	Primary	Lower centrals	Shells of enamel		?	None	None	?	Extracted easily
10.	Turner	1912	Primary	One lower central	Partly formed		?	None	None	?	Fell out after few days
11.	Turner	1912	Primary	Lower centrals	None		?	None	None	?	Present after 14 years

12.	Asana	1921	Primary	Lower centrals	None		?	None	None	Present	Extraction requested
13.	Kennedy	1924	Primary	Lower centrals	Well formed		?	None	None	?	Uppers lost after few days
			Predeciduous	Upper centrals	Small in size		?	None	None	Present	None
14.	Balard	1924	Primary	One lower incisor	None		Twins	None	None	Present	Shed early
15.	Balard	1924	Primary	One lower incisor	None			None	None	?	Died
16.	Horton	1924	Primary	Six upper anteriors	No enamel		2 months premature	?	None	Present	None
17.	Capon	1925	Primary	Lower centrals	None		Twins 4 lb. weight	?	None	Present	None
18.	Capon	1925	Primary	Lower centrals	None			None	None	Present	None
19.	Holt and McIntosh	1940	?	?	None		?	—	—	Present	—
					B. Neonatal						
20.	Herpin	1912	Primary	Lower centrals	None	8 days	Full-term	Papillae	None	?	Lost on tenth day
21.	Herpin	1912	Primary	Right lower central	None	7 days	Not full-term	Papilla	None	Present	None
22.	Cusick	1923	Primary	Lower centrals	Fully developed	14 hours	Refused to nurse	Swelling on gums	None	?	Nursed after extractions
23.	Howkins	1932	Primary	Lower centrals	Well formed	13 days	Good	None	None	Present	None
24.	Cohn and Rector	1935	Primary	Lower centrals	Well formed	2 days	Good	None	None	Present	None

TABLE II.

TOTAL NUMBER OF CASE REPORTS REVIEWED	24
Number of infants born with teeth erupted (natal teeth)	19
Number of infants who erupted teeth during the neonatal period (neonatal teeth)	5
Number of infants with prematurely erupted primary teeth	21
Number of infants with predeciduous teeth	1
Number of infants with unspecified teeth	3
Number of infants with prematurely erupted teeth in the lower jaw	20
Number of infants with prematurely erupted teeth in the upper jaw	3
Number of infants with prematurely erupted lower teeth	20
Number of infants with two erupted lower central incisors	14
Number of infants with one erupted lower central incisor	5
Lower teeth (not specified)	1
Number of infants with prematurely erupted upper teeth	3
Number of infants with upper incisors (central)	1
Number of infants with six upper anteriors	1
Number of infants with upper predeciduous teeth	1
Number of infants presenting symptoms during premature eruption	4
Number of infants with complications	6
Number of infants with a history of other members of the family similarly affected	10

HISTORICAL REVIEW

"Babies born with erupted teeth were known to the Greeks and Romans" (Gates, 1946). Superstitions concerning this phenomenon have varied from claims that such children were exceptionally favored by fate to the belief that they were doomed. Louis XIV, Mazarin, and Richard III are quoted as examples of the former (Fleischmann, 1877; Thoma, 1941). In Poland children born with teeth are considered to be monsters and bearers of misfortune. The latter belief seems to be prevalent in India as well, and a case report was published by Asana in 1921 in which extraction was requested on these grounds.

The importance of this problem had early recognition. Fleischmann in his textbook on pediatrics published in 1877 gave a good summary of twenty cases of natal and neonatal teeth. In 1896 Ballantyne collected case reports of seventy cases of natal and neonatal teeth and presented a paper on the subject before the Edinburgh Obstetrical Society. These two workers adequately described the opinion on the subject prior to 1900. Our own review will attempt to summarize the data since that time.

INCIDENCE OF NATAL AND NEONATAL TEETH

Natal Teeth.—The incidence of natal teeth is probably very low. Howkins (1932) reported only one case in 10,000 births during five years at the Maternity Hospital at Birmingham. Ballantyne (1897) reported only three cases in 17,578 births (1 in 6,000) at the Paris Maternity Hospital between 1859 and 1868 (Table III).

It would be very desirable to determine more accurately the frequency of occurrence of natal and neonatal teeth. Unfortunately, obstetrical records at our disposal were not very clear on this point, so that only verbal estimates could be obtained. The estimate for two of the Chicago hospitals investigated was about one case of natal teeth in approximately 2,000 births (Table III).

Neonatal Teeth.—The occurrence of neonatal teeth is undoubtedly less than the frequency of natal teeth, since during the past half century only

TABLE III. INCIDENCE OF NATAL AND NEONATAL TEETH

NAME OF HOSPITAL	BIRTH RATE	NUMBER OF INFANTS WITH NATAL OR NEONATAL TEETH	RATIO
Paris Maternity Hospital (Ballantyne, 1897)	17,575 in 10 years	3 in 17,578	1 in 6,000
Maternity Hospital Birmingham (Howkins, 1932)	10,000 in 5 years	1 in 10,000	1 in 10,000
Cook County Maternity Hospital (Estimated)	6,000 a year	4 in 6,000	1 in 1,500
Presbyterian Hospital (Estimated)	5,400 in 3 years	3 in 5,400	1 in 1,800

five cases of neonatal teeth were reported compared to nineteen cases of natal teeth (Table I). We could not discover any prevalence study of neonatal teeth in the literature. This is not surprising since pediatric records are only of relatively recent origin, while obstetrical records have been routine over many years. Natal teeth are likely to be discovered by the obstetrician during the course of his routine examination of the newly born infant. The discovery of neonatal teeth before the advent of the pediatrician during relatively recent times was left to the accidental finding by the mother.

TEETH AFFECTED

Tooth Type.—Natal and neonatal teeth have been reported as being predeciduous or supernumerary teeth (Thoma, 1941). However, substantiating evidence to support this view was not found during our review. Of the twenty-four cases of infants with natal and neonatal teeth reported in the literature since 1900, twenty-one infants were described as having true primary teeth (Table I). In one of these twenty-one infants the author (Kennedy, 1924) also reported the presence of predeciduous teeth in the upper jaw. However, the data in that case report are not reliable since the teeth had been lost and the information was obtained from the mother. In one case report, no information regarding the teeth was obtained since they had been removed by the midwife before they could be examined by the attending physician (Magitot, 1883). Two other case reports contained no information regarding the teeth.

According to Brauer and associates (1947), supernumerary natal or neonatal teeth are characterized by their looseness and lack of root formation. This statement is not substantiated by any evidence by the authors. From our review of the literature, it was found that *all* the natal and neonatal primary teeth reported were loose and showed lack of root formation. Thus looseness and lack of root formation cannot be considered diagnostic of supernumerary teeth since true primary teeth are similarly affected.

Tooth Class.—The teeth affected most often were the lower primary central incisors (Ballantyne, 1897). Of the twenty-four cases of infants reported in the literature since that time, twenty infants had teeth erupted in the lower jaw while in three infants the natal teeth occurred in the upper jaw. Two case reports contained no information regarding the teeth (Tables I and II). The apparent discrepancy in total number of cases is due to the fact that one case reported by Kennedy (1924) was an infant with natal teeth in both jaws.

In twenty of the twenty-four cases reported, the infants' natal teeth were lower *central* incisors. Fourteen of the twenty cases were reported to be infants having *both* lower central incisors erupted, while in five case reports only one lower central incisor was reported to have erupted (Table II). Two lower teeth were reported in one instance (Magitot, 1883) but the tooth class was not specified.

In the upper jaw, six anterior teeth were reported at birth in one case (Horton, 1924). Upper central incisors were described by Ballantyne (1897) in one instance, and as mentioned before, one case of an infant with two upper predeciduous teeth was reported to Kennedy (1924). Other teeth, such as cuspids and molars, have been mentioned by Ballantyne (1897) and Fleischmann (1877), and case reports have been cited by these authors.

There is thus a strong tendency for natal and neonatal teeth to be merely *prematurely erupted lower central incisors (usually both).* The strong predilection for the lower central incisors is not surprising in view of the fact that these teeth are normally the first to erupt into the oral cavity.

Occasionally upper primary central incisors may also be erupted at birth. Until actual evidence to the contrary is presented, we may assume that other teeth are very rarely affected.

CLINICAL SYMPTOMS

Symptoms associated with the eruption of neonatal teeth have been described as essentially the same as those found concurrent with normally erupting primary teeth ("teething"). Eruption of teeth during the neonatal period was reported in five of the twenty-four case reports (Tables I and II).

The eruption of the tooth may be accompanied with pain so that the infant refuses to nurse. Other symptoms such as infantile diarrhea, drooling, and malaise have, in some cases, been associated with the eruption of neonatal teeth. However, the presence of these symptoms in infants is a common occurrence and may be associated with the general growth changes occurring in the infant at that period (Fleischmann, 1877; Kruska, 1946).

The newly erupted neonatal or natal tooth is hypermobile (loose) and movable in all directions. This is due to the fact that the tooth is attached only at the neck to the gingiva since root formation is incomplete and bony attachment by gomphosis is not possible. Lack of root formation is easily demonstrated in roentgenograms.

The neonatal tooth may be discovered accidentally during an inspection of the oral cavity. This may be prompted by the infant's refusal to nurse, or by the laceration of the infant's tongue or mother's breast.

Supernumerary and predeciduous teeth should be eliminated from the diagnosis by a careful examination of the roentgenograms. These will usually reveal whether the true primary teeth are still within the developmental crypt. Roentgenograms should always be taken since it is very difficult to make any decision on the basis of tooth form alone.

COMPLICATIONS

Complications were described in six of the twenty-four cases reviewed. Texts and investigators (Fleischmann, 1877; Ballantyne, 1897; Howkin, 1932)

described complications as being infrequent. Cusick (1924) reported an instance of an infant who refused to nurse. Laceration of the mother's nipples resulting in abscess formation have been reported in a few instances. Sublingual ulcerations have been described in a few instances. We have one such case under observation at the present time. Excessive bleeding from around the lacerated gingiva proved fatal in a case described by Magitot in 1883. The bleeding in this case may have been prolonged due to hypoprothrombinemia which is normally present to some extent in the newborn infant from two to five days after birth (Mitchell-Nelson, 1945). Ballantyne (1897) reported two cases of natal teeth with complications. One of these developed necrosis of the alveolar process and died.

Some of the complications which have been described following the premature eruption of the teeth are here summarized:

1. When the teeth are not fully erupted, pressure on them may be painful. This factor may cause the infant to refuse the nipple (Cusick, 1923).
2. The teeth may lacerate the breasts during feeding (Holt and McIntosh, 1940).
3. The teeth are loose and movable in the early stages and there is a constant danger of the teeth becoming detached and either swallowed or aspirated, especially during nursing (Brauer and associates, 1947).
4. Natal teeth may also cause sublingual ulcerations (Ballantyne, 1897). This is probably due to the fact that the tongue in infants lies between the alveolar processes (Brodie, 1940) and the sharp incisal edge of the teeth may lacerate the sublingual surface. Krakovski (1902) reported an instance in which the infant developed an ulceration on the lower surface of the tongue and slept with his mouth open. In the case under our own observation, the infant had a large sublingual ulceration and was very irritable and refused to nurse.

HISTOPATHOLOGY OF NATAL TEETH

It became evident during this review that very little histologic analysis had been made of natal teeth. Little information could be obtained from the clinical descriptions. Ballantyne (1897) found that teeth were soft and almost pultaceous in consistence and they quickly wore down to the level of the gum. In another instance quoted by the same author the teeth became gelatinous and soft. It is possible that in this instance the anomaly may have had some connection with the congenital syphilis present in the case or with its treatment with high doses of mercury which later on resulted in acrodynia.

Horton (1924) reported an interesting case of a Negro baby born two months prematurely with six upper anterior teeth erupted at birth. He described the shape and position of the teeth as good but remarked that they bent under pressure and were devoid of enamel. Schelling (1912) described the natal teeth found in his case as a loose shell of enamel, since while he was extracting them one of them cracked under the pressure of the forceps.

Howkins (1932) was the only person who examined a section of a natal tooth under the microscope. He published two illustrations of the ground section. He said, "It will be seen that the dentin is normal, with the exception of certain irregular spaces in the area of the dentin next to the amelodentinal junction; that is to say in that part of the tooth first calcified, and a slight irregularity in the distribution of the dentinal fibrils. The enamel did not appear to be fully calcified in thickness and the pulp chamber is possibly larger than normal, this being possibly due to the fact that calcification was not completed."

It is hoped that future investigators will pay greater attention to the histologic aspects of this problem.

ETIOLOGY OF THE NATAL TEETH

During our review of the literature it was discovered that although various factors have been suggested as causative in the premature eruption of the primary teeth, none could be well substantiated by either the authors or the data obtained from the twenty-four case reports in the literature. Most of the case reports were lacking in specific data so that no conclusive evidence could be drawn from them.

The following factors have been suggested in various reports and texts as possible causes for this anomaly:

Superficial Position of the Tooth Germ.—Fleischmann, in 1877, while discussing the early eruption of the primary teeth, suggested that (1) the initiation of these teeth began earlier while the successive development was normal, (2) if the initiation were normal, then the growth during the subsequent fetal period was accelerated, or (3) the tooth germ may have been positioned superficially, close to the gingival surface. He further stated that the last was hereditary while the second (normal initiation and accelerated growth) was due to some pathologic changes. These hypotheses seem logical but lack definite proof.

Increased Rate of Eruption During or After Febrile States.—Abels in 1930 formulated the interesting theory that tooth eruption is accelerated during or after prolonged febrile processes. He made his analogy to a general increase in the growth of infants during or after such periods. Clinical observations have shown that growth in length may be relatively accelerated during or after a prolonged rest in bed. Cohn and Rector (1935) further suggested that pyrexia in gravidarum may exert a stimulating effect upon the fetal dentition.

Although this hypothesis, which relates the premature eruption to febrile processes, has not been substantiated by any extensive studies, it may offer a possible explanation and merits further investigation.

Inheritance.—Inheritance seems to play a role in the causation of this anomaly and it has been considered to be a major factor by many authors (Holt and McIntosh, 1940; Capon, 1925; Rosenhaupt, 1911; Herpin, 1912; Ballantyne, 1897). Ten of the twenty-four infants whose case reports were analyzed (41.6 per cent) had other siblings or parents showing the same anomaly (Table I). This degree of association as a familial characteristic is well above chance.

Gates (1946) stated that "the condition (i.e., natal teeth) is probably an irregular dominant, but the irregularity might be due to the presence of an inhibitor or to two genes being acquired."

Holt and McIntosh (1940) reported a family in which natal teeth occurred in members of three successive generations. Capon (1925) reported an instance in which twins were born with two lower central incisors each. Their father also had had teeth present at birth. Balard (1924) reported a case in which twins were born with teeth. Rosenhaupt (1911) described a family in which the oldest son was born with a tooth erupted and the third son with three teeth erupted. The children of the third son had teeth erupted during the second month. Asana (1921) reported the case of two infants with natal teeth born of the same father but by different mothers. Herpin (1912) reported the case of two infants in one family with neonatal teeth.

It may be concluded from a perusal of the literature that natal and neonatal teeth may occur in families and might at times be on an inherited basis. It is to be regretted that most of the case reports lacked specific information in this direction.

The Effects of Congenital Syphilis.—Congenital syphilis, due to its prevalence in the early twentieth century, has been blamed for a large number of dystrophies, and although it is usually associated with retarded eruption of teeth, it has been postulated that it may, in some instances, accelerate the eruption of the primary teeth. Ballantyne (1897) cited two cases of natal teeth which deserve attention. In the first case the teeth sloughed out, the alveolar process became necrosed, and the child died. In the second case the infant developed snuffles and papular rash and was treated with high doses of mercury. The teeth became loose during the treatment and were picked out with the fingers. It may be pointed out that in both instances the symptoms described by Ballantyne resemble those observed in acrodynia, a condition resulting from mercurial intoxication (Warkany and Hubbard, 1948). The complications reported by Ballantyne (1897) may have been caused by excessive doses of mercury used to treat the syphilis rather than by the syphilis itself.

Since only one of the twenty-four cases reported had a history of congenital syphilis and since the incidence of congenital syphilis has decreased, while the incidence of natal teeth has increased during the recent years, it would appear unlikely that congenital syphilis is causative in the premature eruption of teeth.

Endocrines.—"The early eruption of the teeth may be due to hormonal stimulation in abnormal glandular conditions. The hormones of the thyroid, the gonads, and thymus tend to stimulate developmental processes" (Thoma, 1941).

The above statement by Thoma is not substantiated by any evidence. According to Schour and Massler (1945), the eruption of teeth is not hastened by any of the endocrine secretions during fetal life.

Dietary Deficiencies.—The effects of dietary deficiencies on the rate of eruption has not received much attention. Schour and Massler (1945) point out from clinical observations that the eruption of the teeth is accelerated in

scorbutic infants. Other authors report a retardation in eruption. Slobody, Benson, and Mestern (1947) have shown that both the full-term and premature infant have a good vitamin C level at birth, even in cases where the mother's blood serum level was very low. It is unlikely therefore that, even if scurvy does result in accelerated eruption, such a factor would be operative in the newborn infant.

Summation.—With the exception of the familial tendency, all the factors listed above can be discarded easily as unsatisfactory explanations or causes for the phenomenon of natal and neonatal teeth. The familial tendency is striking. Careful attention to genetic factors in future case reports may further elucidate the etiology of natal and neonatal teeth.

MANAGEMENT OF NATAL TEETH

If the tooth is not causing any difficulty to the infant or mother, it should be left alone. It may eventually become firm (Magitot, 1883; Cohn and Rector, 1935). Turner (1912) reported a case of natal teeth which were still present at 14 years of age.

Difficulty may be experienced during nursing if the tooth interferes with suckling at the breast (Magitot, 1883). There is also some danger of a loosened tooth being swallowed. Extraction may be done after careful consideration of the effects of such a loss which, of course, condition such judgment. The risk of laceration of the nipples should not constitute grounds for injudicious extractions. Holt and McIntosh (1940) pointed out the fact that children with normal primary teeth have often been nursed up to 2 to 3 years of age.

Precautions.—(1) If extraction is indicated (as occasionally it may be) proper care should be exercised not to tear the gingival tissue, which is strongly adherent to the tooth substance (cementum). (2) Extraction of natal teeth has been associated with excessive bleeding. Magitot (1883) reported the case of an infant who bled continuously for six days and died. Excessive bleeding during the neonatal period is usually due to the physiologic hypoprothrombinemia occurring at this transitional period. No elective surgery should, therefore, be performed prior to the tenth day of life (Mitchell-Nelson, 1845). (3) The pediatrician should also make sure that the parents are well adapted to the situation and the child is not considered as accursed by some ill omen. Psychological adjustment of the parents to the situation is of great importance for the proper rearing of the infant.

SUMMARY AND CONCLUSIONS

1. A review of twenty-four case reports of natal and neonatal teeth is presented.

2. Natal teeth were found to occur approximately once in 2,000 births in two Chicago hospitals.

3. The teeth affected were of the primary dentition. The lower primary central incisors were reported erupted at or near birth in twenty of the twenty-four cases cited in the literature. Two lower central incisors were

found in fourteen cases while one lower central incisor erupted in five cases. Upper incisors were reported in only three instances.

4. Indiscriminate extraction of these teeth is to be deplored. Complications occurred in six of the twenty-four cases described and deserve consideration.

5. The condition occurs with significant frequency in families. It is possible that some genetic factor is contributory or etiologic. Disease probably has little effect in causing the premature eruption of these teeth.

The problem of natal and neonatal teeth (teeth erupted at birth or during the neonatal period) has rarely been investigated from a scientific point of view, nor have any large number of such cases been followed for any length of time in order to accurately describe the many facets of this condition. This is particularly true of the etiology and the management of the condition. Undoubtedly the condition is regarded as a normal phenomenon by obstetricians and pediatricians and not reported. The problem deserves more than such cursory attention because of its pediatric implications.

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MYOCARDIAL FIBROSIS IN INFANCY

ALEX E. SCHEFRIN, M.D.
PASSAIC, N. J.

THE presence of myocardial fibrosis in infancy is quite uncommon. When extensive it is, more frequently than we may think, a cause of rapid and sudden infant mortality. The causes for such fibrotic replacement are varied and in many cases little understood. Our study of the literature has revealed remarkably few references to the subject of myocardial fibrosis. We wish to add the findings of our case and to correlate them with the meager reports extant in the literature.

D. D., a white female child, 9 weeks of age, was admitted to the Beth Israel Hospital on Sept. 7, 1948, because of a sudden attack of heavy breathing followed by complete collapse. She had been well until ten days before admission when she began to refuse her feedings and became very irritable and feverish. Her temperature was 103° F. A diagnosis of pharyngitis was made, which illness responded quickly to medication. Following her recovery the mother noted frequent periods of irritability and it seemed that the child showed symptoms of colic. Despite formula changes and sedation she continued so until the day before admission, when for the first time she appeared to have had a comfortable day. At 1 A.M. on the day of admission, she suddenly became very pale and began to breathe heavily. She was immediately removed to the hospital.

An examination of the infant revealed severe collapse. There was marked pallor and dyspnea and she lay very still. Her temperature was 94.4° F., respirations 60, pulse 80. Her skin was dry. The fontanel was depressed. The pupils were equal but sluggish. The lungs were clear. The heart was slowed, with the apex beat at the nipple line in the fourth interspace. Heart sounds were regular and rhythmic and no murmur was detected. Her abdomen was soft. No masses were palpated. The liver and spleen were not felt. Extremities were cold but otherwise negative. Neurological examination was negative.

The patient was immediately placed under oxygen and supported with heat and Coramine. A hemoglobin determination taken at this time was 1.95 Gm. and because we doubted that it could have fallen so low, two other determinations were taken by two other technicians. Neither determination rose above 2.3 Gm. Toward morning there seemed to be some response to supportive treatment with plasma and fluids and the temperature had risen to 97.8° F. That afternoon a transfusion of whole blood was given and at 11 P.M. of the first day the hemoglobin had risen to 4.3 Gm. There was definite improvement. Fluids were being taken by mouth in fair quantity. The impression was one of some massive hemorrhage internally, but whether into the intestine or into some retroperitoneal space could not be determined. There had been no hematemesis and a yellow stool had been passed.

The next morning at 7 A.M. there was a sudden reversal. The child became very dyspneic and cyanotic. This was the first appearance of cyanosis. The hemoglobin was now 7.35 Gm. with red blood count 2,800,000. The stools were still yellow. A generalized edema presented itself. Despite supportive measures, including transfusions, the condition of the child remained critical.

On Sept. 9, 1948, two days after admission, several large tarry stools were passed, each stool markedly positive for blood. A blood count taken at this time showed hemoglobin, 8.6 Gm., red blood count 3.2 million with two normo-

blasts, white blood count 20,000, and a differential of 80 per cent polymorphonuclears, 20 per cent lymphocytes. Platelets were 150,000 with a reticulocyte count of 0.9 per cent. Urine showed 2 plus albumin. Bone marrow smears were not abnormal. X-rays taken on this day revealed an enormous enlargement of the heart. The left cardiac contour extended to the left lateral wall of the thoracic cage.

The next day slight improvement was noted, with beginning recession of the edema and a good color response. Fine, crepitant râles with bronchovesicular breathing were present at both bases. On the fifth day there was noted a definite lessening of the edema, and improvement was general. On this day a faint systolic murmur was heard localized in the third interspace to the left of the sternum. Heart enlargement was still marked. Stools were again yellow. Repeated bone marrow studies showed good regenerative response and transfusions were therefore discontinued. Suddenly that evening the child went into collapse and began to have mild tremors and to discharge frothy, blood-stained material from the mouth and nose. Despite active support her condition grew steadily worse and she expired on the eighth hospital day. X-rays taken on the day of expiration revealed the same degree of enlargement of the heart as previously described.

A report of pertinent autopsy findings reads "the heart is enlarged and weighs 34 grams (the norm for this age by the Coppoletta and Wolbach scale is 23 grams). The pericardial sac contains an increased amount of clear fluid. The enlargement is due to hypertrophy of all chambers of the heart. The myocardium of the right ventricle measures 0.36 cm. in thickness, and that of the left 0.6 cm. The myocardium is fairly firm and brown. The foramen ovale is still patent and measures 0.3 cm. in diameter. No congenital anomalies are found. The valves are competent. The coronary arteries are normal and patent. The aorta appears normal. The lungs in all lobes, but particularly in the posterior portions, show fairly firm consolidated dark red areas. Careful dissection of the gastrointestinal tract reveals no gross evidence of the source of bleeding. The mucosa is pale and normal in appearance.

"On microscopic examination there is marked congestion and edema of the lungs. The liver shows considerable fatty change with some focal areas of acute liver cell necrosis and with practically no inflammatory reaction. Sections through the intestines show no significant changes. A number of sections of the heart were made. They show everywhere extensive areas in which the heart muscle is replaced by proliferating connective tissue. Within these fibrotic areas a moderate degree of lymphocytosis and plasma cellular infiltration is noted. Embedded in the connective tissue are here and there islands of muscle fiber with an extensive degree of degenerative changes. Some of the muscle fibers are vacuolated. Sections through the various segments of the coronary arteries show no evidence of sclerosis. Specific stains for glycogen are negative."

Anatomical Diagnosis.—There is recorded extensive myocardial fibrosis of undetermined etiology, hypertrophy and dilatation of all chambers of the heart, small mural thrombi of the left ventricle of the heart, edema and congestion of the lungs, focal interstitial pneumonitis, fatty changes and focal areas of acute necrosis of the liver, and actively hyperplastic bone marrow.

DISCUSSION

Previous to 1933, most enlargements of the heart in infancy were placed in the category of Idiopathic Heart Hypertrophy. It is only since the excellent work of Kugel and Stoloff[1] that an attempt has been made to subdivide this heterogeneous group into its more important components. In a study of fifty-two cases of enlargement of the heart in infants reported at that time,

they set forth the rules under which a true diagnosis of idiopathic hypertrophy of the heart might be established. In this study they classified several cases as myocardial degeneration.

McMahon[2] listed three types of cardiac enlargement in infants. These are: (1) True idiopathic hypertrophy of muscle fiber, (2) Glycogen deposition, which he calls pseudohypertrophy, and (3) An increase in connective tissue appearing as a diffuse myocardial fibrosis.

We shall confine our discussion to the last group.

As early as 1740 Lancisi described enlargement of the heart in embryos associated with damage to and weakness of the muscle fibers. He stated that if these infants had lived, the damage in the myocardium of the heart would have been included in the causes for sudden death.

In a discussion of the pathology, Kugel[4] noted, in a case autopsied by Klemperer, that "macroscopically there are grayish streaks on cutting through the myocardium, with mural thrombi present. Microscopically the myocardium showed focal areas of degeneration. In the vicinity of the fibrous areas there were occasional muscle fibers with vacuoles. Some of the fibers showed atrophy and degeneration with replacement fibrosis. Glycogen disease was ruled out. There are no suppurative foci. Muscle arrangement is distorted."

Weissman[5] reported a case with similar gross and microscopic findings with a definite myocardial fibrosis and perivascular fibrosis but no generalized degeneration of fibers. Scattered areas of myocardial atrophy were present. Eigel[6] also reported a marked increase in the amount of perivascular fibrosis.

These findings are in agreement with the autopsy report we have presented.

Eigel and Lynxwiler[6] described as characteristic the sudden onset of symptoms, including marked cardiac enlargement, dyspnea, cyanosis, vomiting, and sudden death. In a discussion of the anomalous origin of the left coronary artery from the pulmonary artery, a condition which approximates in its course that of our case, Taussig[3] found the condition to be asymptomatic during the first months of life, and said that difficulty in feeding may therefore be the first complaint. This is due to the general debility which results from a failing circulation.

Bland, White, and Garland[7] emphasized pain and symptoms of shock after feedings as outstanding clinical symptoms. They reported a case in which the infant drew up his legs with pain after feeding. Taussig[3] felt that this may have been due to the pain of myocardial ischemia or to indigestion due to generalized weakness secondary to the myocardial insufficiency.

Kugel and Stoloff[1] pointed to dyspnea as one of the early symptoms, further characterized by its sudden appearance. They found that fever was generally absent, even with terminal pneumonia. The chief features of this condition are cardiac enlargement of undetermined etiology, an afebrile course, abrupt onset of symptoms, dyspnea, cyanosis, and absence of signs or history suggestive of congenital heart disease or of other known infection. This usually occurs in a child who has apparently been well.

Almost all of the symptoms mentioned above are found in the case history of our patient with the exception of cyanosis, which could not have been apparent with a hemoglobin determination of 2.3 Gm., since 5 Gm. of reduced hemoglobin per 100 cubic centimeters of circulating blood are necessary for production of visible cyanosis. With no evident bleeding point, we are at a loss to explain the cause for the hemorrhage. It was most likely the cause for the pain and shock present at the onset of illness, and may very well have been secondary to the general myocardial damage present.

As to etiology, Kugel[4] stated that the possible factor of infection was the only consistent one he had noted. McMahon,[2] on the other hand, postulated that these lesions may represent an allergic reaction to milk in a heart that has already been damaged by infection.

Gibson[9] stated that there are probably two chief causes of congenital cardiac anomalies: (1) arrested or imperfect development of the heart in early intrauterine life before the various parts of the heart have been completely differentiated, and (2) fetal disease occurring after the heart has become fully developed. As to the latter, he stated that fetal endocarditis and myocarditis, while much less frequent than the developmental errors, were nevertheless responsible for a certain number of cases. He felt that fetal endocarditis was limited chiefly to those cases in which the mother, suffering from an acute rheumatic infection, transmitted the condition to the child.

Paul,[10] in a study of the literature, found some forty cases of rheumatic fever in infants under one year of age. Most of these were infants being nursed by mothers suffering from acute phases of the disease. There were a few reports of what may have been examples of congenital acquisition.

Richdorf and Griffith[11] reported a 6-day-old infant with polyarthritis in which a culture of the fluid from the infected joints gave an organism which proved to be similar to the *Streptococcus viridans* found in the mother's blood. The absence of local signs indicating a portal of entry after contact, or of other infection, "point toward an intrauterine infection of the infant through the placenta by the organisms circulating in the mother's blood."

Pocock[12] and Schaefer[8] reported a very similar occurrence in infants 12 and 3 days of age, respectively, and their conclusions followed closely that of Richdorf and Griffith.

One symptom, that of massive hemorrhage, has not been previously described. It was to us the most prominent, as the whole picture in the first twenty-four hours suggested that of collapse due to hemorrhage. Despite the precipitous drop in hemoglobin determination to 2.3 Gm., and with full knowledge that hemorrhage had occurred, its location was in doubt for two days until the appearance of tarry stools. Autopsy failed to reveal a focal point for the hemorrhage, not an uncommon lack of finding.

CONCLUSION

From the foregoing information we may draw several conclusions. There appears to be a fairly characteristic symptomatology in these cases of myo-

cardial fibrosis, with the myocardial degeneration as a basis. Thus, we have cyanosis, dyspnea, weakness, difficulty in feeding, and shock. The pathologic findings, too, follow a fairly set pattern, with damage of long standing, and little evidence of recent inflammatory response. The presence of perivascular fibrosis would seem to be of importance.

The etiology is far less apparent. One common and probably most important factor is infection. In none of the cases quoted in the literature was there any suggestion of a presenting infection. In view of the early ages at which many of these infants were autopsied, it would seem that much of the myocardial damage present must have occurred in the prenatal period. We know of no postnatal cause for the marked cardiac changes present at autopsy in our infant.

We are intrigued by the thought that rheumatic fever in the mother could have been responsible for intrauterine infection of the infant, for this mother has a definite rheumatic history, her last flare-up having occurred in 1945. Even though she may be clinically well, we can have no proof that some subclinical infection is not or may not have been present, with greater activity caused by the pregnancy. The reports of Gibson,[9] Paul,[10] and Richdorf and Griffith[11] all favored the concept that rheumatic fever in the infant is entirely possible in prenatal life following active infection in the mother.

SUMMARY

A case of myocardial fibrosis in infancy is presented, together with a report of the literature.

The possibility that myocardial infection with concomitant damage may have taken place during pregnancy is postulated, and it is suggested that there may be some relationship between our findings and a history of fairly recent rheumatic fever in the mother.

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Case Reports

TOXOPLASMOSIS IN A NINE-YEAR-OLD GIRL

PAUL FREEMAN, M.D., AND HELEN B. PRYOR, M.D.
REDWOOD CITY, CALIF.

A CASE of toxoplasmosis in a 9-year-old girl is presented which demonstrates three of the clinical tetrad of signs and symptoms plus a congenital cyst of the left upper lobe of the lung. There is no proved relationship between the lung cyst and the cerebral toxoplasmosis, but a question is raised concerning their probable interrelationship.

Following Frenkel's classification, the case presented was of a patient in the subacute stage, surviving with symptoms of chorioretinitis, cerebral calcifications, and other signs of cerebral damage. The child's mother can be classed as having chronic, latent, asymptomatic toxoplasmosis.

CASE HISTORY

N. H., a white female child, was delivered by a breech extraction on Jan. 23, 1940. The birth weight was 6½ pounds. The prenatal course had been uneventful until about three weeks before term, at which time the mother had had an acute febrile illness with low abdominal pain and a profuse, foul, purulent vaginal discharge. Smear of the vaginal discharge revealed no predominant pathogenic organisms, and the mother recovered before delivery. The placenta grossly contained a mass of cystlike nodules, but no histologic study was made of this material.

The infant was apparently normal at birth, and the routine well-baby checks during the first year of life revealed no abnormalities save a hemoglobin count of 60 per cent at 6 months of age, which responded to iron therapy. However, she was slow in development. She sat alone at one year of age, walked alone at 15 months, and began to talk at about age 2 years.

On Nov. 1, 1944, at the age of 4 years, 8 months, the child became acutely ill with an upper respiratory infection for which she was hospitalized. She was found to have an extensive pyothorax of the left chest (Fig. 1). Thoracentesis was performed with removal of 400 c.c. purulent material. Culture and guinea pig inoculations done on the material revealed no tubercle bacilli, and Mantoux tests using first and second strength PPD were negative. A thoracic surgeon saw the child in consultation and felt that she had either an interlobar pyopneumothorax or a large lung cyst filled with pus. On Dec. 6, 1944, a thoracotomy with rib resection was performed in order to drain the chest. Purulent material continued to drain for about six weeks, after which healing occurred.

The child's course for the next three and one-half years was characterized by frequent febrile illnesses associated with cough and chest pain. Periodic roentgenographic studies of the lung fields consistently revealed an area of rarefaction with a fluid level in the upper lobe of the left lung (Fig. 2).

Because of developing strabismus and progressive loss of vision in the right eye, the child was seen by an ophthalmologist in April, 1945. The mother was told that loss of the vision was the result of scar tissue forming in the eye and that nothing could be done about it. But the child continued to go to school.

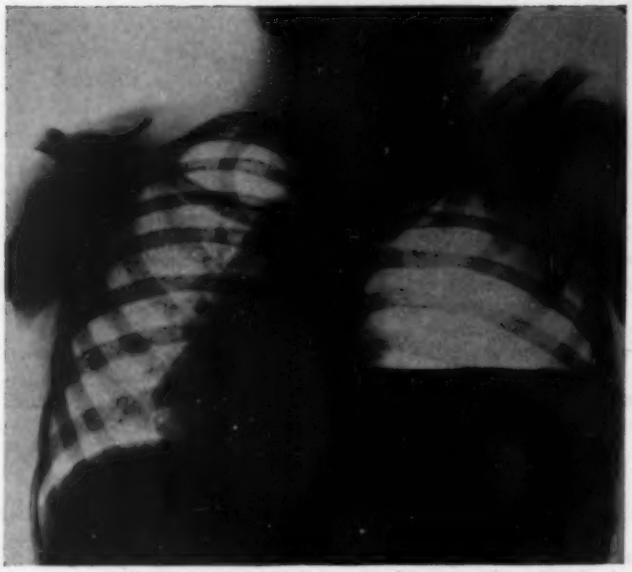

Fig. 1.—Pyothorax left chest displacing heart.

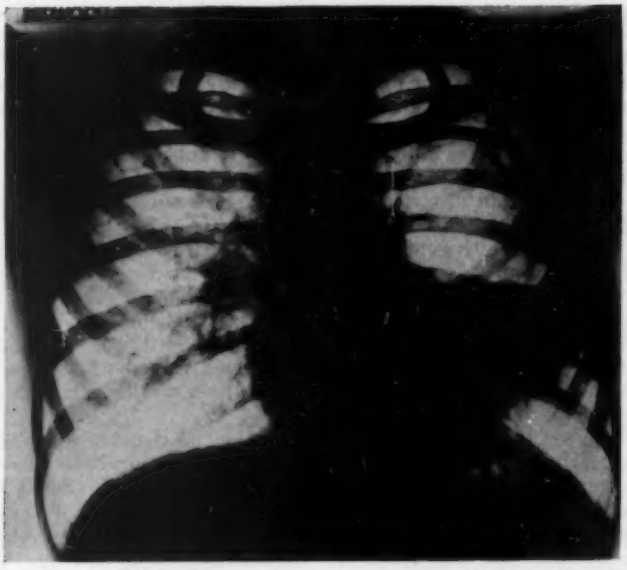

Fig. 2.—Film Aug. 25, 1948, showing fluid level in upper lobe left lung.

An appraisal of N. at this time by her teacher included the following description: "She walked with an ambling, loose-jointed gait. Her shoulders seemed to be held high and her arm motion was jerky. She entered into almost as much play activity as the other children although she walked more than she ran, and didn't run as fast as the others.

"Although she seemed to do all or most of her seeing with her left eye, she held her head straight. She did not seem to strain to see work on the board or on her desk.

"She wrote very lightly and her letters were poorly formed. One might think that lack of strength and coordination in her arms were responsible for such light pressure.

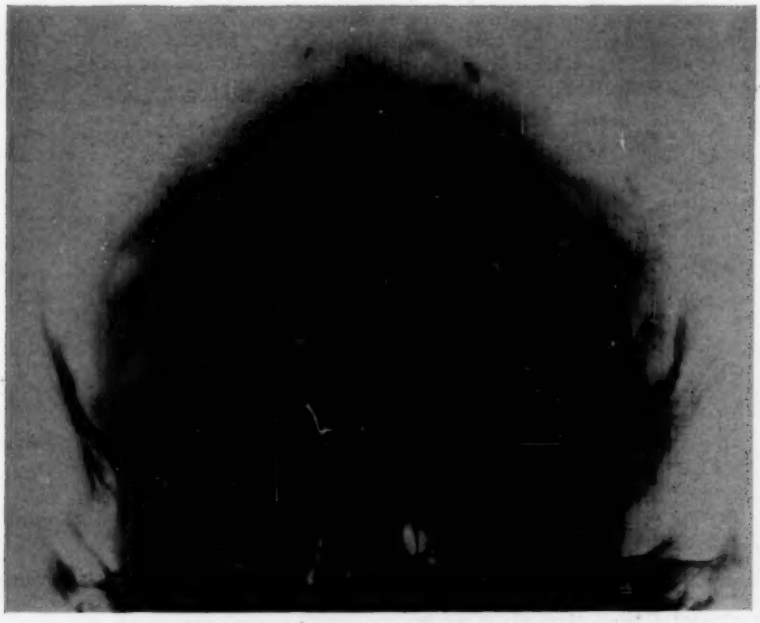

Fig. 3.—Showing several small calcifications in the right cerebral cortex.

"Reading was a blank until suddenly she knew all the words in her first preprimer. After that, she seemed to grasp words; although it was memory or words as a whole and not grasped alphabetically or phonetically.

"Number work was beyond comprehension. She had no interest in it and her conception of numbers was quite retarded. N. was not a daydreaming pupil. She kept busy and did what she could quietly but slowly. She looked quietly happy and not at all frustrated."

On Aug. 25, 1948, during the course of a routine physical examination it was noted that N.'s right fundus was the seat of an extensive chorioretinitis centering about the macular region. The left fundus appeared normal. Also it was found that there was some atrophy of the muscles of her left hand. Roentgen studies of the skull revealed several small calcifications in the right cerebral cortex (Fig. 3), resembling those seen in toxoplasmosis. Because of the chorioretinitis and intracranial calcifications, a tentative diagnosis of toxo-

plasmosis was made and the child was referred to the Uveitis Clinic at the University of California Hospital for confirmation of this diagnosis. There the following tests and results were reported as follows:

Tuberculin, second strength	PPD	neg.
Brucella skin test	4-plus	
Brucella agglutination	—	neg.
Brucella complement fixation	—	neg.
Frei test	—	neg.
Coccidiomycosis, skin test	—	neg.
Histoplasmin, skin test	—	neg.
Staphylococcus antigens	—	neg.
Q-fever neutralization	—	neg.
Toxoplasmosin, skin	plus over minus	

It was also reported that clinical findings on the child were typical of toxoplasmosis, and the failure to obtain a positive neutralization was due to a technical difficulty encountered in her test. A neutralization test for toxoplasmosis performed on the child's mother was strongly positive.

Fig. 4.—Scattered lime salts deposits in fixed brain vary from 0.1 to 2.5 cm. in diameter.

In November, 1948, the child was again referred to a thoracic surgeon for an appraisal of the pulmonary pathology. A comparison of chest films taken at this time with those taken one year previously revealed no increase in the size of the cyst, which measured 9 × 5.3 cm. in the anteroposterior projection. It exhibited about the same amount of fluid, occupying roughly the lower fifth of the cyst. No compression atelectasis of the surrounding lungs was noted, and the thickness of the cyst wall had not increased. The thoracic surgeon felt that this represented a congenital pulmonary cyst which should be removed.

On Dec. 10, 1948, a thoracotomy was done and the entire cyst excised. The cyst was attached along the lateral wall of the thorax, and the principal portion was encased by pulmonary tissue of the left upper lobe. Extensive fibrous reaction and inflammatory adhesions of long standing were encountered at all sites. The child was in good condition immediately after surgery. However, she unexpectedly went into shock on the second postoperative day and expired within a few hours.

The following is a portion of the pathologist's report: "The brain after fixation contains scattered small lime salt deposits which are demonstrated by x-ray and to a less extent grossly. These vary from 0.1 to 2.5 cm. in diameter. There is a narrow, slightly depressed area 7 cm. long in the right cerebral cortex. Beneath this area is a diverticulumlike protrusion of the right lateral ventricle which is 5 cm. in diameter. This is located on a line with the anterior end of the temporal lobe. The brain tissue over this area is only 0.3 cm. thick as compared to 4.5 cm. on the uninvolved side."

Histologic examination: "Brain: There are areas of cortical degeneration with calcification, regional gliosis, and thickened leptomeninges. No toxoplasms are identified, although the changes present are consistent with a diagnosis of healed cerebral toxoplasmosis."

The eye findings in this case will be reported by Dr. Hogan in his series of cases from the Uveitis Clinic at the University of California.

In May, 1949, Dr. Frenkel stated that "about thirty-five cases of toxoplasmosis in human beings have been reported to date diagnosed either by autopsy or animal inoculation."

Cases of toxoplasmosis in children have been reported from North and South America and Europe. There is a wide geographical distribution of the cases in the United States.

Sulfadiazine and Sulfamerazine control experimental toxoplasmosis in animals, but the toxoplasma may persist in the form of pseudocysts in the neural tissues of the host. Other drugs reported by Frankel as successful in treatment of toxoplasmosis include aureomycin, chloromycetin, Polymyxin B, and bacitracin.

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PRENATAL FIBROELASTOSIS ("FETAL ENDOCARDITIS") MANIFESTED CLINICALLY BY TOTAL HEART BLOCK

HAROLD E. STADLER, M.D., F.A.C.P., CHARLES A. REID, M.D., AND HERBERT P. FRIEDMAN, M.D.*
INDIANAPOLIS, IND.

PRENATAL fibroelastosis of the endocardium is a remarkably rare disease. The associated total heart block with lack of a gross cardiac anomaly adds further interest to our case and justifies this report. Previous studies of heart block in infants have shown particularly basic lesions such as interventricular septal defects with or without other gross malformations.

CASE REPORT

R. N. was a 31-year-old para iii, gravida ii who had always been in good health. She had never had rheumatic fever and the only illness which occurred during her pregnancy was a mild rhinitis. This infection was acute and happened at a time when the fetal bradycardia was noted. The last menstrual period was recorded on Feb. 28, 1947. Quickening was noted during July of 1947. One of us (C. A. R.) made the notes which appear in Table I during the pregnancy:

TABLE I

DATE (1947)	BLOOD PRESSURE	FETAL HEART RATE	POSITION	MISC.
July 18	110/65	—	—	—
Aug. 15	110/65	—	—	—
Sept. 12	110/65	72	R.O.A.	U.R.I.
Oct. 10	120/65	72	R.O.A.	—
Oct. 31	130/70	64	L.O.A.	—
Nov. 21	120/60	56	L.O.A.	—
Dec. 2	110/65	56	L.O.A.	—
Dec. 9	110/65	56	R.O.A.	—

The infant, N. N., was born on Dec. 19, 1947, after a labor which lasted fourteen hours. N. N. weighed 7 pounds, 11 ounces at birth. Respiration was quickly established and no abnormality was noted except for a cardiac rate of 60 beats per minute and a soft systolic generalized cardiac mumur. The heart size and contour were normal by x-ray. The electrocardiogram showed a total heart block with ventricular rate of 50 beats per minute.

The infant was observed periodically and no medication was given due to the fact that symptoms referable to the bradycardia were lacking. The weight of the infant was 10 pounds at the age of 2 months. The heart rate was found to be 42 beats per minute when the baby was 2½ months of age. Atropine sulfate was given with resultant drug pyrexia and no change in the cardiac rate.

The patient was admitted to the St. Francis Hospital on March 31, 1948, with a statement by the mother that the baby had suddenly stiffened and screamed incessantly. Cyanosis developed and was progressive. The temperature was found to be 102° F. rectally. The infant died three hours after admission to the hospital.

From the Services of Obstetrics and Pediatrics, St. Francis Hospital, Beech Grove, Ind.
*Doctor Friedman was resident pathologist at the Indianapolis General Hospital, Indianapolis, Ind., at the time of this writing.

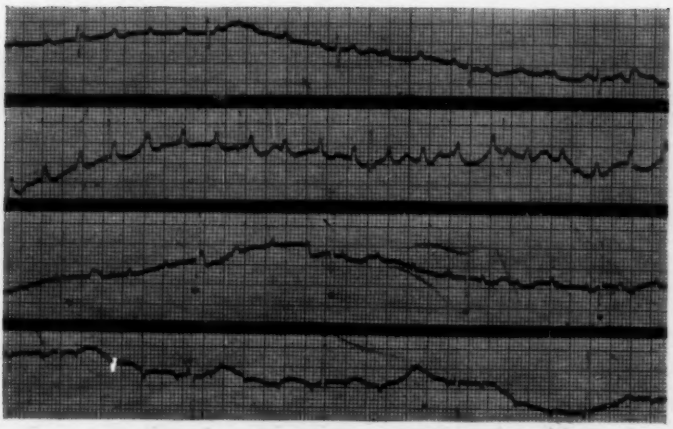

Fig. 1.—Electrocardiogram showing complete heart block.

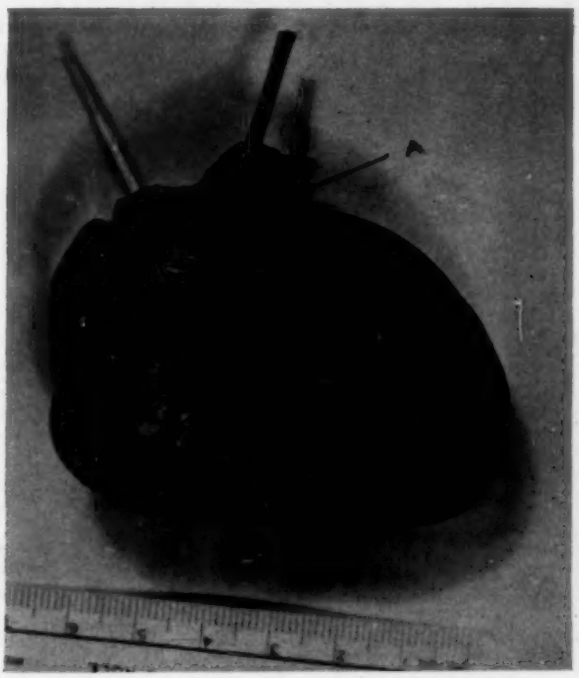

Fig. 2.—Photograph of the heart showing the epicardial lesions. Area *A* overrides the interventricular septum. Area *B* is the large patch of organizing pericarditis on the anterior surface of the heart.

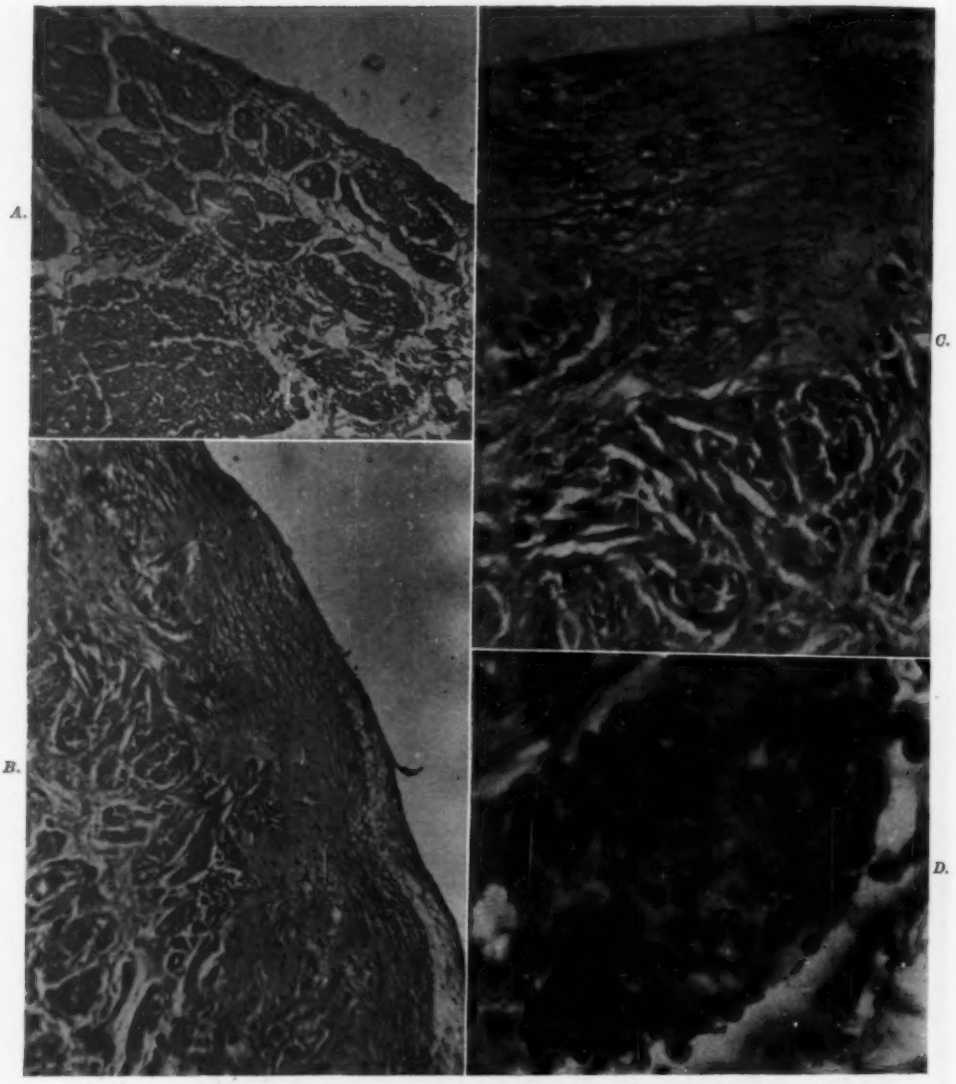

Fig. 3.—*A*, A control slide. *B*, Elastic and fibrous tissue proliferation of endocardium. *C*, Magnified portion of illustration *B*. *D*, Perivascular lymphocytic infiltration from epicardium near the origin of the right coronary artery.

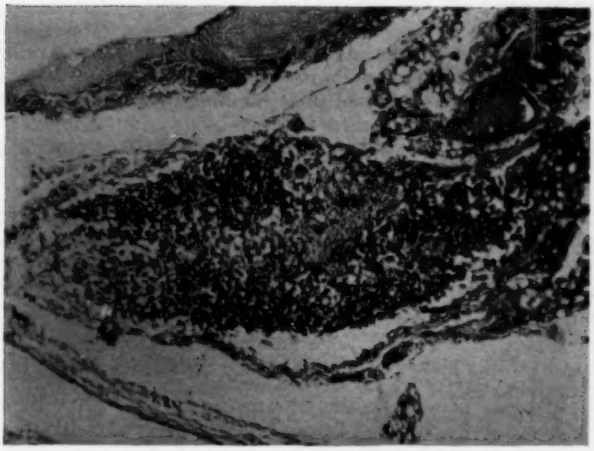

Fig. 4.—Focal area of inflammation of epicardium shown in Fig. 2(*A*). Note endothelial proliferation of vessels, lymphocytes, and large mononuclears.

Fig. 5.—Microscopic section of the plaque of the epicardium shown in Fig. 2(*B*). There is abundant new connective tissue which is very vascular. Inflammatory cells are sparse and consist of small cells and macrophages. (×250.)

Necropsy was performed exclusive of the head, but spinal fluid obtained post mortem was clear. The essential visceral changes were those of passive congestion. The heart was enlarged and weighed 80 grams. A patch of puckered epicardium with smooth surface and measuring 1.5 cm. in diameter appeared over the anterior aspect of the right ventricle. There was moderate hypertrophy of both ventricles, but particularly of the right, and also marked dilatation of the right atrium and right ventricle. The foramen ovale admitted a small probe, but was functionally closed. The valve leaflets showed a moderate diffuse fibrous thickening, but no retraction was present and there was no evidence of functional derangement. Sections were taken serially through the entire septum perpendicular to the axes of expected bundle branches. Sections were also taken in the same plane above the septum in the region of the sinoauricular node, the area of the epicardial thickening noted above, right and left ventricular walls, and various valves.

Microscopic study failed to disclose any tissue sufficiently distinctive to be identified as conductive in nature. The following changes were noted: the areas of thickened epicardium showed a focal increase in fibrous tissue, marked vascular proliferation, and a few round cells; in the supporting tissue containing the cardiac nerve plexuses between the aorta and pulmonary artery, anteriorly immediately overlying the sinoauricular node there was a nodular lesion consisting of proliferating blood vessels, fibrosis, and exudate made up of a moderate number of histiocytes and lymphocytes; the vessels in general showed a moderate hyperplastic intimal thickening; occasional vessels were surrounded by a loose connective tissue containing a few angular cells suggesting Aschoff cells; the endocardium was diffusely but irregularly thickened due to an increase in elastic connective tissue, the thickening was more marked at the base of the valve leaflet; the valve leaflets showed a marked cellularity with increase in number and density of connective tissue fibers.

DISCUSSION

Anderson[1] speaks of endocardial fibroelastosis as being manifested by cardiac enlargement in infancy followed by cardiac failure of the congestive type. He adds that the heart is three to five times the normal weight, globular in form, and showing marked dilatation of the left ventricle. Anderson also observed thickening of the left ventricle and less frequently of the right ventricle, and thick white appearance of the endocardium lining the right ventricle particularly.

Weinberg and Himelfarb[2] reported two cases of fibroelastosis of the endocardium which occurred in siblings. The absence of maternal infection during pregnancy, the lack of inflammatory changes in the cardiac structure, and the appearance of the disorder in siblings led the writers to find agreement with the concept of a developmental defect. The explanation for the ventricular failure offered in this paper deserves close attention. It is postulated that the arterioluminal flow into the myocardium is reduced due to the development of the elastic changes with production of myocardial anoxemia. The dilatation of the myocardium and its subsequent failure would thus be explained by the development of the endocardial fibroelastosis which has constricted and possibly eventually brought about obliteration of the vascular channels essential to the normal function of the myocardium.

Sano and Anderson[3] reported a case of elastic tissue hyperplasia of the endocardium of the left side of the heart associated with narrowing of the anterior cusp of the mitral valve in a 5½-month-old boy infant who had not shown evidence of cardiac disease before his terminal illness. It was the conclusion of these writers that the process of elastic tissue hyperplasia was "developmental rather than infectional."

Gross[4] stated that the occurrence of fetal endocarditis has never been established and "that the assumed etiologic pathogen in the reported cases has been either anamnestically absent or variable in identity." He further observed that the valvular endocardial changes seen in those cases were better explained on the basis of a developmental defect since no inflammatory residual was found. The case report in this writing included a pathologic summary showing stenosis of the mitral and aortic valves and marked diffuse endocardial sclerosis of the left ventricle. There was also hypoplasia of the aortic root, rudimentary development of the left ventricular cavity, and the presence of a large patent ductus arteriosus.

We feel that the two areas of pericarditis described are significant and the result of an inflammatory process which is "essentially burned out" and approaching the stage of healing. These areas are certainly small but nevertheless clues to what may have been initially a widespread inflammation. The associated bradycardia in this case (to our knowledge never previously reported) gave the only indication of a cardiac disorder and pathologically we can only postulate impingement on the conduction bundles by the endocardial fibroelastosis. The widespread cardiac changes in this case would certainly not allow such a glib explanation as a "functional conductive block." We are convinced that the pathologic changes described here are basically those of a prenatal inflammatory process.

SUMMARY

A case of endocardial fibroelastosis is presented which was manifested by bradycardia. The absence of maternal illness as well as absence of systemic illness on the part of the infant do not militate against a diagnosis of "fetal endocarditis" as shown by pathologic sections here. The theory of Weinberg and Himelfarb is a reasonable explanation for the cause of the death of the infant.

The authors are indebted to Paul N. Harris, M.D. of the Lilly Laboratories, and to Irving H. Zitman, M.D., Chicago, Ill., for their help in the preparation of this manuscript.

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TYPHOID FEVER IN AN INFANT COMPLICATED BY TYPHOID MENINGITIS

Therapeutic Failure With Chloromycetin; But Response to Aureomycin

Howard W. Ripy, M.D.
Nashville, Tenn.

THE rarity of typhoid fever in infants under 2 years of age has been well established.[1-3] Even more infrequent is a true typhoid meningitis with isolation of the typhoid bacilli from the spinal fluid.

The discovery of Chloromycetin opened a new avenue for the treatment of typhoid fever. Woodward and associates[9] were the first to employ Chloromycetin to treat this disease in human beings. They observed dramatic and progressive improvement in all of ten patients treated, the fever subsiding on the average of within three and one-half days, positive blood cultures becoming negative, and the patients improving rapidly. Two of their ten patients developed relapses which responded promptly to a second course of Chloromycetin therapy.

Various reports[10-13] of the efficacy of this agent in the treatment of typhoid fever substantiating Woodward's original observations have been published.

The opportunity recently presented itself to observe and treat typhoid fever in a 13-month-old Negro female child. Her disease apparently failed to respond to Chloromycetin treatment, and she developed typhoid meningitis. With the addition of aureomycin to the treatment, clinical and bacteriologic response was prompt and dramatic. Her case history follows. (Also see Chart I.)

CASE HISTORY

O. A. B., a 13-month-old Negro girl, was admitted to Nashville General Hospital on July 10, 1949, with the chief complaint of coma. Her history was vague and obtained with difficulty from her grandmother. Her illness had begun eight days before admission when she developed moderate diarrhea and occasional vomiting. There was a persistent fever, and six days before admission she became lethargic, semicomatose, and at times irrational and delirious. Lethargy persisted, and gradually she became more comatose, being able to be aroused only occasionally to drink milk.

She had received no immunizations, and recently she had been visiting in the country where she had drunk unboiled well water.

Admission physical examination revealed a well-nourished and well-developed Negro female infant in moderately deep coma, arousing only to painful stimuli. She was acutely and seriously ill. Rectal temperature was 104° F. Her skin was well hydrated and without lesion. Her head showed normal fontanel. Her eyes revealed equal pupils which reacted sluggishly to light; her ears, nose, and throat were clear. Her neck was moderately stiff. Her lungs were clear and her heart normal with a pulse of 120 per minute. Her abdomen was soft without mass or palpable viscera. Neurological examination showed sluggish deep tendon reflexes, positive Kernig's and Brudzinski's signs, and marked general hypotonia, slightly greater on the right, with movements elicitable only with deep pain.

From the Department of Pediatrics, Vanderbilt University School of Medicine, Nashville.

ADMISSION LABORATORY DATA

Blood.—Red blood cells, 4.67 million per cubic millimeter; hemoglobin, 9.6 Gm. per 100 milliliters; white blood cells, 4,600 per cubic millimeter, with a differential of 3 per cent juveniles, 8 per cent stabs, 62 per cent segmented neutrophiles, 25 per cent lymphocytes, and 2 per cent monocytes. Kline test for syphilis, sickling preparation, and malaria thick drop smear were negative. Nonprotein nitrogen, blood sugar, calcium, and inorganic phosphate were within normal limits.

Urine.—Urine was negative.

Lumbar Puncture.—On admission spinal fluid was produced under normal pressure with 3 lymphocytes per cubic millimeter, sugar of 89 mg. per cent, chlorides of 680 mg. per cent, and protein of 15 mg. per cent. Culture grew hemolytic *Staphylococcus aureus* which was thought to be a contaminant.

Skin Tests.—Old tuberculin was negative 1:1,000. Histoplasmin was negative 1:100.

X-rays.—X-rays of the chest and long bones were negative.

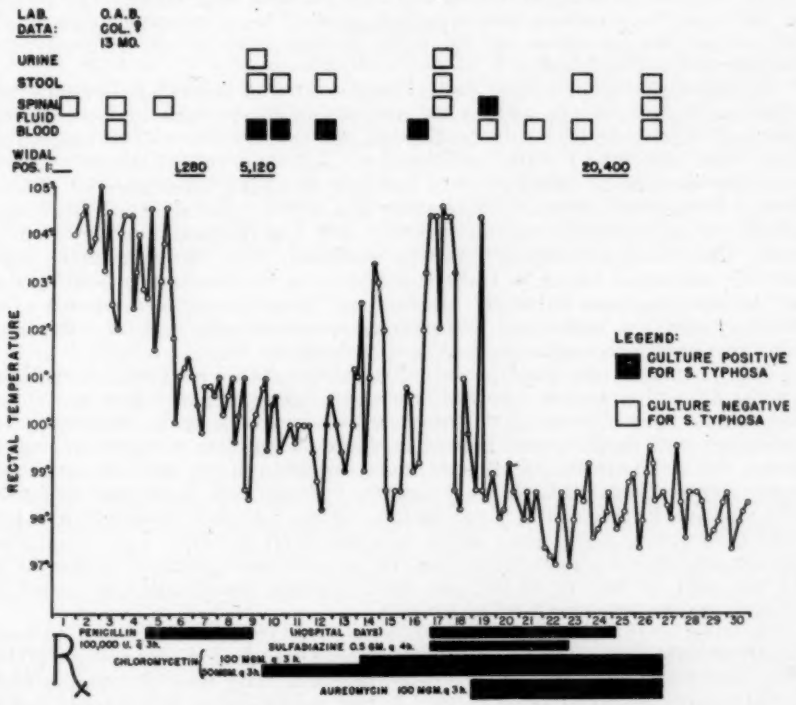

Chart I.—Clinical summary of cultures, temperature chart, and treatment of infant through course of typhoid fever complicated by typhoid meningitis.

COURSE IN HOSPITAL

The working diagnosis was encephalopathy, cause undetermined. She was given a liquid diet by gavage, and received sponges for fever. She continued to have a spiking fever varying between 102° and 105° F. for five days,

and her semicoma and apparent paresis persisted although she became more responsive to painful stimuli. On the third hospital day the lumbar puncture was repeated, revealing 6,000 red blood cells per cubic millimeter and 5 white blood cells per cubic millimeter. The culture was sterile. Repeated two days later, spinal fluid showed 6,000 red blood cells per cubic millimeter, 18 white blood cells per cubic millimeter (10 polymorphonuclear and 8 mononuclear), sugar of 104 mg. per cent, protein of 33 mg. per cent, and negative smear and culture. On the fourth day the initial spinal fluid culture was reported to show hemolytic *Staph. aureus,* and although it was thought to be a contaminant, she was placed on penicillin 100,000 units every three hours. This was continued until the second spinal fluid culture failed to produce growth.

On the sixth hospital day agglutinations against *Salmonella paratyphi, Proteus vulgaris OX-19, Brucella suis,* and *Pasteurella tularensis* were negative. The Widal agglutination was positive 1:1,280 and against *Salmonella schottmülleri* positive 1:80. She was isolated and given a high-protein, high-caloric gavage feeding. On the eighth day Widal agglutination was again positive 1:5,120. Blood, catheterized urine, and stool cultures were made. The following day her blood culture was reported positive for a gram-negative motile bacillus, and she was given (on the tenth hospital day) 50 mg. Chloromycetin every three hours by mouth.

On the sixth hospital day, before treatment was instituted, her lethargy began gradually to disappear and her paresis and encephalopathic attitude disappeared. Her temperature subsided and for the next four days ranged between 100° and 101° F. She continued to require gavage feedings and had transitory periods of lethargy. On the day following institution of Chloromycetin therapy her highest temperature was 100° F., and she clinically began to improve more rapidly, became playful, alert, and responsive to her environment. She no longer required gavage feedings. Over the next three days, however, she again began to spike fever until on the fourteenth hospital day her temperature was 102.4° F. A blood culture made thirty-six hours after Chloromycetin was begun was still positive for *Salmonella typhosa.* Repeated three days later, blood cultures again grew *S. typhosa.*

On the fourteenth hospital day with temperature rising and with blood cultures remaining positive, the Chloromycetin dosage was increased to 100 mg. every three hours by mouth. However, blood culture again repeated after the dosage was doubled still showed *S. typhosa,* but her temperature fell to normal for twelve hours, then once more began to spike, and on the seventeenth day reached 104.6° F. She became irritable and developed stiff neck with positive Kernig's and Brudzinski's signs. Lumbar puncture was performed, revealing 1,896 white blood cells per cubic millimeter of spinal fluid (90 per cent polymorphonuclear and 10 per cent mononuclear), sugar of 46 mg. per cent, protein of 49 mg. per cent. Gram's smear failed to reveal organisms, and culture produced no growth.

In view of the pleocytosis, stiff neck, and fever, she was placed on penicillin, 100,000 units every three hours and oral sulfadiazine, receiving 0.5 Gm. every four hours in addition to the Chloromycetin. Her fever dropped to 98.6° F., but promptly spiked again to 101° F. and the following day reached 104.4° F. The lumbar puncture was repeated showing 179 white blood cells per cubic millimeter (73 per cent mononuclears and 27 per cent polymorphonuclears), sugar of 78 mg. per cent, and protein of 78 mg. per cent. The culture subsequently grew *S. typhosa.*

Because of her failure to respond to Chloromycetin and with the development of typhoid meningitis and the persistence of typhoid bacteriemia, treatment was augmented by aureomycin, 100 mg. every three hours by mouth.

Her temperature immediately and dramatically fell to normal, ranging between 97° and 99.8° F. for the remaining eleven days of hospitalization. Clinically she remained well, alert, responsive, and continued to eat an adequate diet.

Blood cultures taken two, four, and seven days after addition of aureomycin to the treatment regime were sterile. Lumbar puncture performed five days after beginning aureomycin revealed 102 white blood cells per cubic millimeter of spinal fluid (65 per cent mononuclears and 35 per cent polymorphonuclears) with a sugar of 69 mg. per cent and a protein of 53 mg. per cent. The spinal fluid culture was sterile. On the twenty-second hospital day sulfadiazine was discontinued, and two days later penicillin was stopped. On the twenty-fourth day agglutinations showed Typhoid H negative and Typhoid O positive 1:20,480. Repeated stool and urine cultures were negative for *S. typhosa.*

On the twenty-seventh hospital day Chloromycetin and aureomycin were discontinued, the child having been afebrile and asymptomatic for eight days. Three days later she was discharged fever-free and clinically well.

DISCUSSION

The apparent failure of Chloromycetin in this case is difficult to explain. There has been no evidence yet reported that bacteria develop resistance to Chloromycetin. Unfortunately no tests were made on the organism isolated from the child to determine its sensitivity to the various antibiotic agents. In Woodward's[9] cases, however, the bacteria cultured from two patients in relapse were demonstrated to be as sensitive to Chloromycetin in vitro as were the organisms originally isolated. No large series of cases treated with Chloromycetin have been reported, and accordingly no valid conclusions can be drawn regarding the effectiveness of this agent against varying strains of *S. typhosa.*

After an adequate trial it was believed that Chloromycetin was having little effect on the typhoid infection present in this infant. Although she improved clinically, typhoid bacteriemia persisted even after the dosage of Chloromycetin had been doubled. Fever continued, and she developed typhoid meningitis while receiving Chloromycetin. It was thought advisable to add aureomycin to the regimen, and the response both clinically and bacteriologically after beginning aureomycin was dramatic, the fever subsiding within twelve hours and the bacteriemia and meningitis clearing.

Long and associates[14] used aureomycin to treat five patients with typhoid fever and reported recovery in all, with blood and stool cultures reverting to negative. They felt, however, that the defervescence and general improvement of their patients were equivocal and concluded that Chloromycetin was superior to aureomycin for the treatment of this disease.

The clinical improvement manifested in this child after first instituting Chloromycetin therapy, and again temporarily after increasing the dosage, would seem to demonstrate that the drug had some beneficial effect on the disease. This would apparently indicate infection with a relatively resistant strain of *S. typhosa,* the emergence of a resistant or mutant bacterial population, or perhaps only a partial bacteriostatic activity of the drug.

The more complete response noted after the addition of aureomycin introduces the problem of complex therapy. It has often been demonstrated that two antibiotic or chemotherapeutic agents used in conjunction with each other can be capable of producing a greater combined bacteriostatic effect. Aureomycin itself has been shown to be effective in vitro against *S. typhosa,*

and the report of Long and associates[14] seems to substantiate its use clinically in human infections. Whether or not the response noted in this child after the addition of aureomycin was due to that drug alone or to a combination of both aureomycin and Chloromycetin cannot be ascertained.

SUMMARY

A case of typhoid fever in a 13-month-old Negro female infant, complicated by the development of typhoid meningitis, and failing to subside with Chloromycetin, but responding promptly upon the addition of aureomycin, is reported.

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OSTEOGENESIS IMPERFECTA CONGENITA

Report of a Case in a Negro Infant

Roland B. Scott, M.D., and Clinton H. Wooding, Jr., M.D.
Washington, D. C.

OSTEOGENESIS Imperfecta is a rare developmental defect of the mesenchyme. Unusual fragility of bone is the most characteristic clinical finding in this interesting syndrome, which may include blue scleras, deafness, and relaxation of the ligaments. The condition has been variously described in the literature as fragilitas ossium, osteopsathyrosis, and Lobstein's disease.

According to the time of appearance of symptoms, the disease may be separated into prenatal and postnatal types. The former is termed osteogenesis imperfecta congenita, and multiple fractures are usually evident at birth. In the postnatal varieties, fractures first occur in infancy (osteogenesis imperfecta infantilis) or later childhood (osteogenesis imperfecta tarda, osteopsathyrosis).

A dominant mendelian hereditary trait has been observed in the late type; however, the exact etiology of the disease is unknown. More cases have been reported in female than in male children. The influences of race is apparently unknown. Leading pediatric textbooks[1] and comprehensive articles[2] in the English literature make little or no reference to the occurrence of the condition in the Negro. Only one case of osteogenesis imperfecta congenita has been observed among the 11,818 Negro newborn infants delivered at Freedmen's Hospital during the ten-year period from 1938 to 1948.[3] The following case is reported because of the apparent great rarity of this disease, particularly in the Negro race.

CASE REPORT

B. H., a 6-day-old Negro male infant, was admitted to Freedmen's Hospital on June 30, 1948, because of deformities of the skull and extremities. The infant was born at another local hospital. The mother enjoyed good health throughout her pregnancy. Labor and delivery were reported as normal and uneventful. The infant weighed 7½ pounds at birth. The mother was 23 years old and in good health. The only other sibling, a 23-month-old girl, was apparently normal. The family history was negative for bone fragility, blue scleras, deafness, syphilis, consanguinity, and hereditary conditions.

Physical examination revealed a poorly developed but fairly well-nourished infant in no acute distress. Palpation of the skull elicited a boggy, crepitant sensation, most marked in the occipitoparietal regions. There was a bilateral prominence of the temporal regions. The neck appeared to be unusually short. The left external ear (auricle) was directed downward and outward, placing it at a lower level than its fellow on the right. The scleras were bluish but not a deep indigo. The ocular fundi, lungs, heart, abdomen, and genitalia all appeared normal.

Severe gross deformities were observed in both upper and lower extremities which presented abnormal curvatures and apparent shortening. (Fig. 1.) Roentgenograms of the skull (Fig. 2) showed poorly calcified islands of bone in a lacunar or mosaic pattern. In addition there were multiple fractures involving the clavicles, the rib cage, and all of the long bones of the upper and lower extremities. (Fig. 3.) Callus formation was observed in many sites

From the Department of Pediatrics of Howard University College of Medicine and the Pediatric Service of Freedmen's Hospital, Washington, D. C.

surrounding healing fractures. There was generalized osteoporosis. The long bones presented many abnormal curvatures associated with apparent shortening of the shafts.

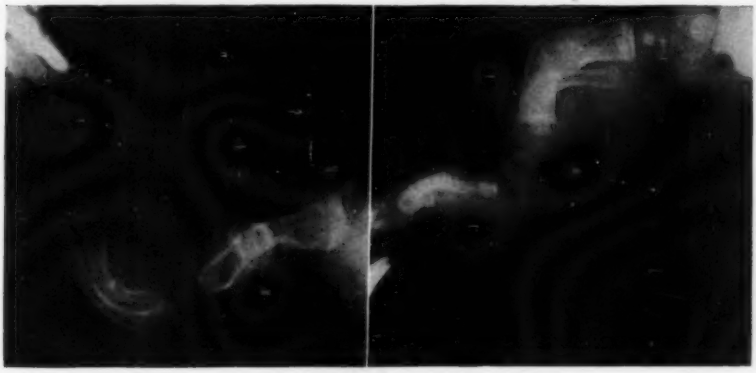
The hemogram and urinalyses were normal. The blood Wassermann was negative. The serum calcium and phosphorus were 11 mg. and 6.8 mg. per cent respectively. Alkaline phosphatase was 6 Bodansky units. The infant's

Fig. 1.—Photograph of infant demonstrating abnormal curvatures and deformities of extremities with apparent shortening.

course in the hospital was uneventful. He gained weight normally on routine feedings and was discharged on Oct. 18, 1948, at the request of his parents.

The infant was seen in the outpatient department one month after discharge. His condition appeared satisfactory at that time. On June 27, 1949, the infant developed an acute attack of dyspnea and died suddenly at home. Autopsy was not performed.

Fig. 2.—Roentgenogram of the skull and thorax. Islands of bone may be seen forming a lacunar pattern in the frontal and parietal regions. Arrows point to fractured clavicle and humerus. There are multiple fractures of the ribs.



A. *B.*

Fig. 3.—Roentgenogram of bones of *A* upper and *B* lower right extremities, showing fractures and abnormal curvatures.

DISCUSSION

This infant exhibited the usual physical and roentgenographic findings of osteogenesis imperfecta congenita. In the differential diagnosis congenital rickets and syphilis were excluded on the basis of the history, physical examination, and laboratory data.

The apparent shortening of the extremities presented by this infant bore a superficial resemblance to chondrodystrophia. This dwarfing of the extremities in the prenatal form of osteogenesis imperfecta may be attributed to stress (uterine contractions) operating on an inherent osteomalacia[2a] leading to bending, intrauterine fractures, and secondary angulation with resultant shortening (dwarfing) of the long bones. Moreover, the typical mosaic pattern observed roentgenographically in the skull, together with the multiple fractures in the clavicles, ribs, and long bones, definitely exclude chondrodystrophia.

There is no satisfactory specific therapy for osteogenesis imperfecta. Afflicted infants should be carefully protected to avoid fractures. When fractures occur, they should be promptly treated to prevent deformity. The fractures usually heal rapidly. Therefore care should be taken to avoid prolonged immobilization which results in atrophy and increased fragility.[4]

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Psychologic Aspects of Pediatrics

LATERAL DOMINANCE

Right- and Left-Handedness

Harry Bakwin, M.D.
New York, N. Y.

UNDER normal circumstances the manual skills, the language functions (speaking, reading, and writing) and, to a less extent, sighting and pedal skills are controlled mainly by one side of the brain, the other side functioning in only a rudimentary manner. In right-handed persons, the left hemisphere is dominant whereas in left-handed individuals, the right hemisphere leads. This unilateral control is a special attribute of man. The preferential use of one side of the body is occasionally seen in animals, but it is poorly developed and can readily be altered.

Even in man, however, unilateral cerebral dominance relates only to the language functions and to the more intricate manual and pedal skills, the relation of the two hemispheres to one another being quite different for the simpler activities. Thus a lesion in the cerebral cortex on one side will give rise to a paralysis of voluntary motion on the opposite side and the same is true for the sensations of pain, temperature, touch, and kinesthesia. But even manual skills are by no means limited to one hand. What the preferred hand can do, the other hand can do also. Thus in the playing of stringed instruments of the violin group, the "fingering" is done with the left hand and the bow is held with the right. It is generally considered that manipulation of the bow is the more difficult task, requiring the most elegant control. The movements required of the left hand, too, are intricate, but they are readily acquired by right-handed individuals with practice. It is not known whether or not ambidexterity is an asset to a string instrumentalist.

Unilateral dominance appears early in life. Giesecke[1] observed the manual activity in infants from birth through 17 months of age. She found that, in individual infants, the movements of the hands were regularly more frequent on one or the other side and a differentiation could be detected shortly after birth. Moreover, there was a positive correlation between the amount of spontaneous activity of the hands during early life and the preferential use of the hands in reaching for objects in later infancy, indicating that these are related phenomena. Records of head turning and spontaneous movements of the legs also showed a lateral preference. There was evidence of changes in dominance for the individual child which took place at fairly definite age levels, notably during the seventh month and again at the 10-month age levels. Giesecke's observation that shifts in dominance take place during the first year of life has been confirmed by other workers.

From the Department of Pediatrics, College of Medicine, New York University-Bellevue Medical Center, New York.

Gesell and Ames[2] found that, even in children who later established a clear-cut right-handedness, marked shifts in handedness take place from age to age, particularly striking during the first year of life. There is a tendency for "contact and manipulation of objects to be first with the nondominant hand, then bilateral, then with the dominant hand alone, once again bilateral, then with one hand, usually and increasingly the dominant. As 18 months in many children there comes a period of marked bilaterality followed by definite use of the dominant hand at 2 years." But even after this, as late as 7 years of age, there is a transient period of use of the nondominant hand or of both hands together. Nearly all children follow this sequence, but the fluctuations take place at different ages and there is varying emphasis of the successive stages.

In the studies of Gesell and Ames, the test object used to elicit behavior was of considerable importance. Thus, in responding to the pellet, behavior at all ages was predominantly unilateral whereas responses to the bell might at the same time be bilateral.

According to Gesell and Ames the earliest manifestations of handedness are in some way bound up with the tonic-neck-reflex. When the newborn infant turns his head to one side, the arm and leg on that side are automatically extended, the opposite arm is bent at the elbow, and the leg is bent at the hip and knee. When the infant turns his head to the other side, the position of the limbs changes accordingly. The tonic-neck-reflex is observed as early as the twenty-eighth week after conception. It disappears gradually. Normally at 12 weeks after birth it is less conspicuous than earlier; at 16 weeks it is in transition, and at 20 weeks it is replaced by symmetrical arm and leg movements. Its persistence beyond this age indicates serious disease of the brain.

The tonic-neck-reflex is, as a rule, predictive of later handedness; but there are exceptions. In the series of nineteen children studied by Gesell and Ames from early infancy up to 10 years of age, the direction of the tonic reflex was definitely predictive of later handedness in fourteen children, and in five of the nineteen children it was ambiguous or contradictive. In four instances left-handedness was correctly foretold by a predominant left tonic-neck-reflex in early infancy.

THE ORIGIN OF LATERAL DOMINANCE

Opinions differ as to whether hand preference is determined primarily by heredity or by environment. That there is a hereditary basis for handedness is indicated by the observation of Gesell that the right tonic-neck-reflex, which is related to handedness, is already present in the 28-week-old fetus; and by the studies of Giesecke on the relation of unilateral movements during the neonatal period and early infancy to handedness later on. Difficult to explain on an environmental basis alone is the presence of left-handed persons in a dominantly right-sided society.

Environmental pressure is a potent but secondary factor determining the choice of the master hand. Recent archeological studies of implements used in the Stone Age show that hand preference among aboriginal man was about

equally divided. During the Bronze Age a marked shift toward right-handedness took place and the trend has continued up to the present. Contemporary primitive groups have a higher proportion of left-handedness than more highly developed societies.

Blau[3] contends that hand preference is an acquired, learned trait. The acquisition of knowledge, skills, and modes of behavior depends on these three cardinal elements: (1) the capacity to learn, (2) proper educational opportunities, and (3) the wish or emotional urge to acquire such learning. Sinistrality may arise on the basis of some handicap which interferes with the individual's adjustment to one or more of these three essentials of the learning process:

1. As obvious examples of sinistrality on the basis of incapacity to learn, Blau mentions those who have lost the use of their right arms. In addition there are persons with strabismus or serious visual deficiency of the right eye with consequent use of the left eye as the dominant one. He attributes the high incidence of left-handedness among the mentally defective to their failure to develop from the original bilaterality of infancy and their general poor response to training.

2. Faulty education. Since Blau contends that the origin of dextrality depends on the encouragement of dextral tendencies, it is evident that if this encouragement is absent, left-handedness is as likely to occur as right-handedness. In some instances the acquisition of left-handedness may be actively encouraged. Where the parents themselves are left-handed the child may acquire the left-handed habit through imitation and identification, and he may then be encouraged in this usage. The trait may be acquired in the same way from a nurse, from an older sibling, or from other persons who frequently are with the child. Instances have been reported where a left-handed teacher unconsciously influenced first-grade pupils to use their left hands.

At times a child may acquire left-handedness by imitating, with the complementary hand, the hand movements of an adult sitting opposite to him, as in the eating situation. Some children are actually taught to use the left hand by a parent who mistakenly assumes that her child is left-handed.

3. Blau is of the opinion that negativism is a frequently disturbing factor in the acquisition of right laterality. Sinistrality is a product of the young child's resistance to suggestion and command.

INCIDENCE

Estimates of the incidence of left-handedness vary widely. The difficulty in reaching accurate conclusions is due to the presence of individuals who show no striking predilection for one or the other hand. The larger the number of tests used in making the diagnosis, thereby including more and more unlearned activities, the higher is the proportion of sinistrals. According to the most reliable surveys, 6.6 per cent of male adults and 3.8 per cent of female adults are left-handed. The incidence is much higher in children, decreasing gradually as adulthood is approached. Moreover the sex difference is not as striking in children as in adults. Girls acquire dextrality earlier than boys do.

Left-handedness is more frequent in mentally defective children than in those of normal mentality, and it is acquired later. There is, too, a higher

proportion of sinistrality among criminals and geniuses. The incidence of left-handedness among twins, both mono- and dizygotic, is about the same or slightly greater than in the general population.[4]

TRAINING FOR HANDEDNESS

The question as to whether a child with left-handed tendencies should be encouraged in this usage or whether efforts should be made to convert him to right-handedness is one which is being actively debated at present. Nielsen[5] is of the opinion that the side of the brain which will lead is hereditarily determined and that handedness is established in this way. However, the functional capacity of both halves of the brain is the same at birth and it is for this reason that the minor hemisphere can take over full function in cases of severe injury to the major hemisphere in early life.

An important application of this knowledge has been made by Phelps[6] in the management of the child with hemiplegia. He has observed that the incidence of seizures, mental deficiency, speech difficulties, and behavior disorders of all types is much greater in children with right hemiplegia than in those with left-sided paralysis. He attributes this to involvement of the dominant hemisphere which would naturally be the case much more frequently in right hemiplegics. He therefore urges, contrary to prevalent practice, that the uninvolved extremity be manipulated so as to encourage transfer of dominance to the uninjured half of the brain and, at the same time, to give no exercise whatever to the affected arm unless one is certain that it is not the dominant one.

Contrary to the opinion of most neurologists, Blau contends that cerebral dominance is determined culturally. The potentiality for one or the other cerebral hemisphere to lead is an inherent human property, but the choice of which side is to dominate depends on the experiences of the individual. Early handedness sets the location of the cerebral language centers.

Since both schools of thought agree that the choice of the master hand by the young child can, under certain circumstances, determine which side of the brain will lead, it seems reasonable to encourage the use of one or the other hand, preferably the right, in children who appear to use both hands with equal or nearly equal facility, so that cerebral dominance will be established in one or the other cerebral hemisphere. Orton[7] advises that, in the group of children who are not developing a selective skill in either hand or in whom the balance is close, the skill and habit of use of the hand which has the greater capacity be increased. In many instances there is no apparent harm from training on the two sides, but it seems likely that even the very skillful ambidextrous individual would have been more facile had he been trained electively in accordance with his natural bent.

Blau advocates training all children to the use of their right hand. In a right-handed world there are many disadvantages to being left-handed. Lighting and seating arrangements in classrooms are designed for right-handed writing. Our written language is constructed for right-handed reading and writing. Many tools and other implements are more easily used with

the right hand. Left-handedness may be socially uncomfortable, as at the crowded dinner table. He believes that the change may be made even after left handedness has become well established. If the child desires to make the change and will cooperate, he should be assisted.

Eustis[8] would train children in whom the left-handed trait is weak to the right hand; but, if the preference for the left hand is strong he recommends against forcing the child. He believes that the danger of producing stuttering by teaching an apparently left-handed child to use his right hand has been exaggerated. Stuttering, appearing under these circumstances, is as likely to indicate an inherent weakness in the speech mechanism which breaks down under the strain of conversion, as it is to mean a shift in the speech center to the originally nondominant side of the brain.

Contrary to the view expressed by Blau, we believe that once hand preference is definitely established, no attempt should be made at conversion. The naturally left-handed child will usually be less successful with the right hand in such activities as writing, games of skill, and the use of tools. The child should not merely be allowed to develop his own natural handedness; he should receive active encouragement. Left-handed children are often permitted to use the preferred hand but do not receive the training accorded children who are right-handed, although their need for training is actually greater, since they must face a multitude of influences which tend to make them right-handed. Few children are so strongly left-handed that they are able to resist these influences entirely. In this extremely right-handed world, left-handed children need active help in order to assist them to realize their full potentialities. There is some reason to believe that the mirror form of writing, i.e., from right to left, is the natural one for left-handed individuals and that the left-handed child must acquire an orientation and progress in writing opposite to that which is easiest for him. In addition, the writing paper is frequently put in front of him in the same position as for a right-handed child, which forces him to adopt a cramped and awkward position. He should be aided also in acquiring the proper slant for his letters since most left-handed children prefer to write backhand, i.e., to slant the letters with the tops toward the left.

Evidence of conversion from left-handedness may be obtained through study of the handwriting, which may be difficultly legible and irregular with frequent reversals. Sometimes the child can write more legibly with the right hand from right to left (mirror writing) even though there has been no previous training or practice. Again certain children can write better with the eyes closed than while they are watching the writing hand. In the converted sinistral, fatigue during writing is likely to come early and the necessary effort may detract from the content of the work.

EYEDNESS

Eyedness refers to the selection of the eye which is habitually used for sighting. The human eye is equipped with two seeing mechanisms, peripheral vision for the rapid scanning of a broad field, and central vision for more ac-

curate and detailed reception. The peripheral visual fields are equipped like the motor centers and unilateral lesions to the appropriate tracts give rise to hemianopsia. For central or macular vision both hemispheres act together as a unit and stimuli received by either eye are fused into a single impression. Cortical blindness results only when both hemispheres are injured. Though information regarding hearing is not as precise as that for vision, it appears that a similar mechanism is operative and both hemispheres may serve interchangeably with each other.

It has been suggested that the sighting eye determines the master hand and that left-eyed individuals who are right-handed are converted sinistrals. Orton[7] disagrees with this view and points out that it fails to explain the occurrence of right-eyedness in some left-handed individuals. Moreover, the same proportion of right- and left-handedness exists among the congenitally blind as among the seeing.

Since sighting is dependent on the skill of the extraocular muscles rather than on clarity of vision, defects in vision have little influence on the choice of the master eye unless the refractive error is considerable. The eye is less often subjected to training procedures than the hand, although many naturally right-eyed microscopists train themselves to use the left eye in order that the right eye may be free to control drawing or note-taking while looking into the microscope.

A number of tests for eyedness have been described. The simplest and the one which gives fairly consistent results when repeated on different days is performed as follows: A hole about one-half inch in diameter is made in a stiff piece of paper. This is handed to the child and he is requested to look at the examiner's finger or other object through the hole. The child will usually use the master eye for this purpose. The paper may be placed in the patient's right hand, then in the left hand, and finally in both hands. Several trials should be made each time. This test will usually reveal a definite preference for one or the other eye. In some instances, however, the child will use the right eye when the paper is held in the right hand, the left eye when the paper is held in the left hand, and will show indecision when the paper is placed in both hands, indicating that there is no strong eye preference.

Footedness, like eyedness, is much less likely to be influenced by training than handedness, and hence the determination of footedness may be of some value. The preferred foot is used for kicking, starting up a flight of stairs, mounting a bicycle, etc. The chosen foot usually corresponds to the master hand but this is by no means constant.

INTERGRADES

There exists a graduated series from the strongly right-handed to the strongly left-handed with all degrees of ambidexterity in-between; and the same relates to eyedness. A striking mixture of right- and left-dominance is seen in the combination of right-handedness with left-eyedness. There may also be greater skill with the large muscles of one shoulder as in ball throwing and preference for the small muscles of the opposite hand as in writing. Although this is most commonly observed in converted sinistrals, it may also

occur when there is no frank intermixture of right- and left-patterns but the child is able to use both sides equally well in many different activities.

PROBLEMS ASSOCIATED WITH ALTERATION IN LATERAL DOMINANCE

These depend on the completeness of the left-handedness, on the attempts at conversion, on the attitude of the child toward his deviation, and on the attitude of other persons toward him.

There is reason to believe that children without dominant handedness are more likely to have reading disability than those who are definitely left-handed.[9] The handicaps which may develop in this group have been described by Wile[10] and are here listed:

1. Defects in writing, including illegibility, slowness, mirror writing, and reversal of figures.
2. Speech deficiencies, including slow utterance, unclear speech, stuttering, and late development of speech.
3. Specific reading disability and spelling difficulty.
4. Physical maladjustments owing to difficulties in muscular coordination, including instability and motor restlessness, awkwardness, poor coordination, and heightened fatigability.
5. Emotional unrest, feelings of inadequacy or inferiority.

Children who are strongly left-handed and left-eyed usually resist conversion successfully. They suffer only as they find themselves different from others. Children prefer to be like other members of their group and any difference is likely to be looked upon as unfavorable. A left-handed child is frequently teased and chided and may develop a feeling of inferiority. His clumsiness and awkwardness may increase this feeling and various associated difficulties may result. In some instances there may be poor achievement in writing and other skills because of inadequate training.

Wisely,[11] in his study of school children, found that whereas only 6 per cent of right-handed children were repeaters, 12 per cent of left-handed children and 15.8 per cent of those who had been converted from left- to right-handedness were repeaters. This indicates clearly that left-handedness presents a definite school problem.

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Comments on Current Literature

A NEW SOLUBLE SULFONAMIDE*

THE remarkable advance in antibiotic therapy within recent months has eclipsed somewhat the importance of the sulfonamide drugs. There are still, however, many uses for the sulfonamides in the routine practice of medicine. One of the serious drawbacks in sulfonamide therapy has been renal complications associated with precipitation of the drug in the tubules and pelves of the kidneys and in the ureters. While the measures generally advocated for the prevention of urinary difficulties, such as employment of sulfonamide mixtures, alkalinization, and forcing of fluids are helpful, they do not eliminate entirely the hazards of sulfonamide treatment.

A new sulfonamide drug of comparatively high solubility with no loss in therapeutic efficiency is a welcome addition to the physician's armamentarium. Several recent reports[1, 2] indicate that the sulfonamide compound, 3, 4-Dimethyl-5-Sulfanilamido-Isoxazole (Gantrosan or Gantrisin), is such a drug. Comparative studies have revealed that at pH 6 Gantrosan (Gantrisin) is soluble to the extent of 350 mg. per 100 c.c., in contrast with 60 mg. per 100 c.c., or less, for sulfadiazine and sulfamerazine. This striking increase in solubility in relation to pH was demonstrated further by concentration studies of normal urine:

> Gantrosan (Gantrisin) is soluble to the extent of 60 mg. per 100 c.c. at pH 5.4 and 327 mg. per 100 c.c. at pH 6.14, whereas sulfadiazine is soluble, 12.9 mg. per 100 c.c. at pH 6.3 and 300 mg. per 100 c.c at pH 7.5 or 8.0. The solubility of sulfadiazine approaches that of Gantrosan (Gantrisin) only after the pH of the urine is raised to 7.5 or 8.

Adequate level of the new drug in the blood is maintained consistently for six hours following administration. The spinal fluid level of Gantrosan was found to be about one-third that of the blood level. The greater part of the drug is excreted in the urine within forty-eight hours, the most rapid excretion occurring in the first eight hours.

Gantrosan can be administered by the oral, intravenous, subcutaneous, or intramuscular routes. The dosage for children is calculated proportionate to age on the basis of 1 grain per pound of body weight for each twenty-four-hour period, one-half of the twenty-four-hour dose being given as the initial dose (total dose of 0.13 Gm. per kilogram body weight per twenty-four hours).

The clinical results indicate that the new drug is effective in the treatment of a number of infections and has a therapeutic range comparable with that of sulfadiazine and sulfamerazine. Brickhouse and his associates[1] report excellent results in the treatment of pneumococcic pneumonia, Klebsiella pneumonia, gonococcic meningitis, meningococcic meningitis, and of infections due to beta hemolytic streptococcus and *Hemophilus influenzae*. Good results were obtained with urinary tract infections due to *Escherichia coli, Aerobacter aerogenes,* and *Pseudomonas aeruginosa.*

*Gantrosan (or Gantrisin), a product of Hoffmann-La Roche, Inc.

Of 142 patients treated, crystalluria was reported in one patient, and in another patient, gross hematuria occurred on the second day of intravenous therapy. The hematuria persisted for twelve hours and disappeared in spite of the fact that drug therapy was continued.

Svec and his co-workers[2] used Gantrosan in the treatment of 300 patients with no evidence of renal damage. Other toxic manifestations reported consisted of dermatitis, drug fever and nausea and presented no serious problem.

On the basis of information available at the present time, Gantrosan (NU-445; 3, 4-Dimethyl-5-Sulfanilamido-Isoxazole) is a valuable adjunct to our present methods of therapy and "is recommended for use when a sulfonamide is required in a patient where renal complications must be particularly guarded against."[1] Results in the treatment of diarrhea, especially shigellosis, will be of interest.

RUSSELL J. BLATTNER

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News and Notes

The Sixth International Congress of Pediatrics

The Congress, as previously announced, will be held at Zurich, July 24 to 28, 1950. A scientific exhibition will be held in conjunction with it which will open July 21 and close July 31. During the five days of the Congress there will be two plenary sessions daily, and, in addition, twelve group sections on such subjects as the newborn infant, virus diseases, social medicine, blood diseases, and surgery in childhood.

The local committee of arrangements has announced that each participant in the Congress *must* obtain an "All-Inclusive Congress Arrangement." This includes:

1. Congress Card A, B, or C (see below).
2. Hotel accommodations at Zurich, including breakfast and lunch or dinner. These begin with dinner July 23 and end with breakfast July 29.
3. Gratuities in connection with the hotel.
4. Transportation between station and hotel.

The charge for the "arrangement" varies with the accommodations provided. It varies from 250 Swiss francs for a single room without bath in a pension, to 433 francs for a single room with bath at a "de luxe" hotel, with three gradations in between. The charge for similar double rooms varies from 250 to 406 francs per person. Items of a personal nature as beverages and laundry are not included. As of Jan. 15, 1950, the rate of exchange was $23.40 for 100 Swiss francs.

Every person attending must have a Congress Card A, B, or C.

Card A—100 francs (included in "arrangement") includes all activities—meetings, receptions, official banquet, and an excursion on the lake of Zurich.

Card B—60 francs, for accompanying ladies.

Card C—40 francs, is limited to attendance at medical sessions and exhibits.

The committee has designated the American Express Company as its "official and exclusive transportation agency." The "All-Inclusive Congress Arrangement" will be sold by the American Express Company at its agencies throughout the world and cannot be obtained elsewhere. The Company will also handle steamer, air, and railroad reservations to and from Zurich if desired. It will also furnish aid in obtaining visas for the passport, foreign exchange, and the like, and will have a special banking and travel office at the University building where the sessions will be held. It has agencies in twenty-five of the larger cities in the United States and Canada where the "All-Inclusive Arrangement" can be obtained.

Plans are being made for a number of post-congress tours to European pediatric centers. Data is not as yet available.

Attention is called to the heavy travel to and from Europe this summer in view of the Holy Year pilgrimages to Rome. Transportation is already difficult to obtain except for the higher priced steamship accommodations.

Official delegates to the Congress, representing the four national pediatric organizations, are as follows:

American Academy of Pediatrics: Drs. Rustin McIntosh and Oliver L. Stringfield.

American Medical Association, Section on Pediatrics: Drs. Margaret M. Nicolson and Adolph G. deSanctis.

American Pediatric Society: Drs. L. Emmett Holt, Jr., and A. Ashley Weech.

Society for Pediatric Research: Drs. Henry L. Barnett and Robert Ward.

The members of the American Committee will represent the United States at the Executive Session of the Congress. They will also be glad to assist in any way possible those who plan to attend or participate in the Congress or the Scientific Exhibit.

Program for the Congress

July 21: Opening of the scientific and industrial exhibition. Opening of the public exhibition organized by the World Health Organization, the International Red Cross and the International Union for Child Welfare.
July 21 and 22: Advanced lectures, partly intended as introduction to the group lectures.
July 23 (in the evening): Official reception.
July 24, A.M.: First Plenary Session.
From July 24, P.M. to July 27: Group lectures of which from six to seven will be held simultaneously.
July 27, P.M.: Excursion on the Lake of Zurich.
July 28, A.M.: Second Plenary Session.
July 28, P.M.: Group lecture held conjointly with the International Union against Venereal Disease.
July 28 (in the evening): Banquet.
July 28 and 29: Advanced lectures.
July 31 (evening): Close of the exhibitions.

Dr. John P. Hubbard resigned the directorship of the Committee for the Improvement of Child Health of the Academy of Pediatrics as of March 1, 1950. Dr. Hubbard will become associated with the National Board of Medical Examiners as Associate Secretary and will take over the positions of Executive Secretary and Medical Secretary upon the retirement of Everett Elwood and Dr. Stewart Rodman in the near future. He has also been appointed professor of preventive medicine at the University of Pennsylvania Medical School.

The **University of Minnesota** announces a continuation course in pediatrics April 10 to 12, 1950. This course, which will be presented at the Center for Continuation Study, is intended for physicians specializing in pediatrics and will be devoted to disorders of metabolism and endocrine function.

Distinguished visiting physicians who will participate as faculty members for the course are Dr. Daniel C. Darrow of Yale University School of Medicine, New Haven, Conn., and Dr. George M. Guest, Children's Hospital, Cincinnati, Ohio. The remainder of the faculty for the course will be made up of clinical and full-time members of the staff of the University of Minnesota Medical School and the Mayo Foundation.

The **American Board of Pediatrics** has announced that in addition to the three examinations listed under News and Notes in the January issue of THE JOURNAL, an examination will be held in Cincinnati on May 5, 6, and 7, 1950. A change has been made in the date of the San Francisco examination to June 30, July 1 and 2, 1950. This follows immediately after the meeting of the Section on Pediatrics of the American Medical Association rather than preceding it, as was announced previously.

The annual award of the **Rocky Mountain Pediatric Society** was given this year to Dr. Elmer L. Timmons of Colorado Springs for his long and outstanding service to pediatrics. Dr. Timmons has been in practice for forty-four years and organized the Colorado Springs Baby Clinic in 1924.

The **Rocky Mountain Pediatric Society** announces that the following officers were elected for 1950:

President: Dr. Joseph Lyday.
Vice-President: Dr. Mariana Gardner.
Secretary-Treasurer: Dr. Edwin T. Williams.

Book Reviews

From the Hills. An Autobiography of a Pediatrician. John Zahorsky, M.D., St. Louis, 1949, The C. V. Mosby Company, 388 pages. Price $4.00.

Dr. Zahorsky at the age of 75 retired in 1947 from an active pediatric practice in St. Louis to live in the Ozark mountains where he spent his boyhood. Here he has busied himself with an autobiography which the reviewer has found of great interest. When he was a baby, his parents emigrated from Hungary, and after six years in Cleveland, settled on a farm near Steelville, Mo. The chapters telling of his boyhood years in the Ozark country, and of the efforts and the obstacles he overcame to obtain an education, are among the most interesting in the book. In 1892, he entered Missouri Medical College, which was later incorporated into the Washington University School of Medicine, and was graduated three years later. Dr. Zahorsky has minimized his medical experiences throughout the book, but, nevertheless, it gives a good picture of the medical school, medical practice, and of the city fifty-odd years ago, and of a type of pediatric practice that is fast changing. Much stress is placed on his associations with and the influence of Dr. E. W. Saunders who was one of the most unique characters in pediatrics, and with the Bethesda Hospital of which he was President of the Board from 1933 to 1946. The one thing that reveals itself most strikingly throughout the autobiography is Dr. Zahorsky's love for nature. This love for the Ozark hills, its farms, trees, and even the weeds, stands out as the dominant note in the character of the man. It is this love which is reflected in a busy, successful medical life of many years.

B. S. V.

Morbus Caeruleus: An Analysis of 114 Cases of Congenital Heart Disease With Cyanosis. Edited by E. Manheimmer, Basel, 1949, S. Karger, 332 pages, 122 figures. Price 40 francs (Swiss).

In this monograph are presented data from the diagnostic work-up of 114 patients with cyanotic heart disease. The presentation of the material is preceded by a short chapter on the embryology of the human heart and blood vessels which gives the essentials of embryonic development in a very understandable form. In the succeeding chapters the material is critically analyzed and presented from the standpoint of differential diagnosis and treatment. The various types of clinical and laboratory examinations are fully discussed. The chapters on roentgenological examination and angiocardiography are particularly well done and well illustrated.

This book will be of a great deal of interest to pediatricians who are particularly interested in the problem of congenital heart disease as it gives a very good bird's-eye view of the complete work-up which can be expected to be of value in the differential diagnosis of cyanotic heart disease.

CARSON.

American Pediatric Directory, 1949-1950. Edited and published by Joe T. Smith, M.D., Knoxville, Tenn., 254 pages. Price $7.00.

The fourth edition of the directory published by Dr. Smith is far more complete than previous editions. Biographic data given under state and city residency makes up most of the volume. This is followed by an alphabetical listing of pediatricians. We are amazed to find over 6,000 physicians listed as "pediatricians." Included, however, are many who do not wholly restrict their practice, and a large number of recent graduates now in hospital training. It does show clearly the tremendous growth of interest in the field of pediatrics. The brief data and the up-to-date addresses make it of particular value at the present time when there have been so many changes since the war.

Editor's Column

IRON POISONING

REPORTS[1, 2, 3] in the British literature within the past three years of six instances of acute poisoning from the accidental ingestion of large quantities of medicinal iron by children emphasize a potential danger which is not generally appreciated. The significance is evident from the fact that in five of the six instances there was a fatal outcome, death occurring within one to three days after ingestion. The victims were infants and small children who mistook for candy a tablet form of a proprietary preparation containing ferrous sulfate and small amounts of copper and manganese sulfates.

Experimental studies[1, 4] in animals indicate that it is the iron salt and not copper or manganese which is responsible for tissue damage. As in the fatal cases in children, death, when it occurred, took place within a relatively short time after ingestion. Recovery in the nonfatal cases appeared to be complete. The principal pathologic change was necrosis of the gastric mucosa with hemorrhage into the stomach. In the submucosa there was polymorphonuclear infiltration, and hemorrhages were observed between the muscular layers. Changes in the liver varied from cloudy swelling to focal necrosis. The changes observed by Forbes[1] in human cases appear to be more marked than those observed by Somers[4] in animals. The possibility that the damage in the liver and kidney is secondary to shock resulting from destruction of gastric tissue is considered. The speed and apparent completeness of recovery lend support to such a hypothesis.

The toxic dose of iron has not been accurately determined, but the lethal dose for an adult male based on weight in relation to the estimated lethal dose for a rabbit would be as much as several hundred tablets containing 0.2 Gm. of ferrous sulfate.[4] The lethal dose for small children, however, would be calculated in tens and not in hundreds of tablets. In the recorded fatal instances in which the number of tablets was known or estimated, it ranged from fifteen to fifty tablets.

In view of the widespread use of iron preparations for the treatment of anemia and because of the palatability of the liquid preparations and of the attractiveness of the tablets, which may simulate confections, it would seem essential for physicians to be aware of the dangers of overdosage. The omission of reference to iron as a poisonous agent in the texts of pediatrics now in use in the United States which list poisonous agents[5] should be corrected. The comments in the various texts not only attest to the value of iron in hypochromic anemia, but in general emphasize its low toxicity. References are made in most of them to occasional evidences of gastrointestinal irritation.*

The treatment of iron poisoning is not well defined. To be effective it would have to be instituted promptly after ingestion. The damage to the gastric

mucosa seems to be the most significant factor and is related to the quantity of iron ingested. Early lavage would thus be indicated. The subsequent introduction of milk and egg white has been recommended. Somers,[4] on the basis of observations that iron in Blaud's pills was less toxic than in other tested preparations, gave sodium carbonate with toxic doses of ferrous sulfate to rabbits and found that either life was prolonged or recovery occurred. The possibility that sodium carbonate, if given sufficiently early, might be beneficial is suggested. BAL[3] has not lessened the toxicity in animals but rather appears to aggravate the toxic effects of ferrous sulfate and ferric chloride.

Iron preparations should be kept out of the reach of infants and small children.

W. E. N.

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DR. JOHN P. HUBBARD

THE item in News and Notes of Dr. John P. Hubbard's retirement from the ICH directorship of the Academy of Pediatrics is of more than passing interest. As director of the Survey of Child Health Services and Pediatric Education from 1945 to 1948, he carried out to a successful completion the most outstanding pediatric effort that has ever been undertaken. His executive ability, his patience, and his persistence in carrying through the difficult task of the survey earned the respect and admiration of medical leaders far beyond the field of pediatrics. We wish him the greatest success in the positions he has accepted. The pediatricians are deeply in his debt.

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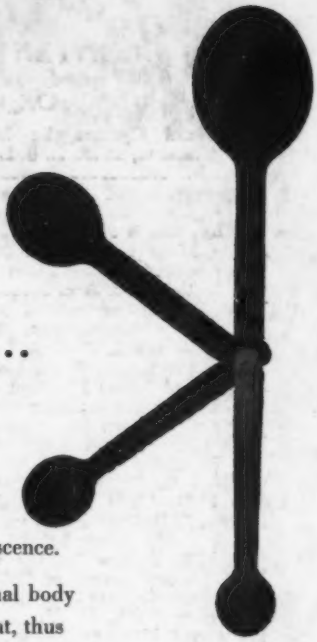

starting point for all feeding problems...

Almost every type of infant formula can be simply made when Dryco is used as a starting point. Dryco is a versatile formulation which serves as a basis for designing special diets for healthy infants or during illness and convalescence.

In itself Dryco assures ample protein intake for optimal body growth and tissue development. Dryco provides less fat, thus minimizing the danger of digestive disturbances. Carbohydrates may be added when indicated, and the fat content may be modified by adding milk (fresh, evaporated or dried) to the formula.

Moreover... Dryco's special drying process makes it more easily digested than the fresh milk from which it is made.

Dryco supplies more minerals, particularly more calcium, than a corresponding formula of whole milk.

Dryco contains those vitamins in fluid milk which are essential for infant health and growth. Only vitamin C need be added.

Dryco is made from spray-dried, pasteurized, superior quality whole milk and skim milk, providing 2500 U.S.P. units of vitamin A and 400 U.S.P. units of vitamin D per reconstituted quart.

Each tablespoonful supplies 31½ calories. Readily reconstituted in cold or warm water. Available at pharmacies in 1 and 2½ lb. cans.

Dryco® *a versatile base for "Custom" formulation*

The Prescription Products Division, The Borden Company, 350 Madison Avenue, New York 17